# The American Journal of Cardiology

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### **FEBRUARY 1, 1990**

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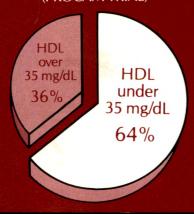


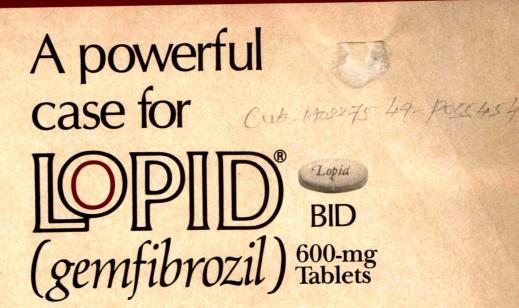
## Market Control of the Control of the

## What's a common denominator of most heart attack victims?

Mixed hyperlipidemias—elevated cholesterol and triglycerides—are common among heart attack victims,<sup>1</sup> and nearly two-thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.<sup>2</sup>

HEART ATTACK PATIENTS (PROCAM TRIAL)<sup>2</sup>





### Raised low HDL 25%

—in patients whose baseline HDL was below 35 mg/dL in the landmark Helsinki Heart Study (HHS).3

### Reduced heart attack incidence\* up to 62%

—in these HHS patients and 45% in HHS patients whose baseline HDL was below the median (46.4 mg/dL). Incidence of serious coronary events was similar for LOPID and placebo subgroups with baseline HDL above the median (46.4 mg/dL).<sup>3</sup>

### Raised HDL levels 1½ to 3 times more effectively than lovastatin

—in a 12-week, double-blind, randomized trial among patients with moderate to severe hyperlipidemia. Lovastatin achieved greater reductions in total serum cholesterol than gemfibrozil in this study population.4

### RAISES HDL DRAMATICALLY REDUCES HEART ATTACK

LOPID is indicated for reducing the risk of coronary heart disease (CHD) in Type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequestrants and nicotinic acid.

\*Defined as a combination of definite coronary death and/or definite myocardial infarction.

References: 1. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. J Clin Invest. 1973;52:1533-1543. 2. Assmann G, Schulte H. PROCAM-Trial: Prospective Cardiovascular Münster Trial. Zürich: Panscientia Verlag; 1986:8-9. 3. Data on file, Medical Affairs Dept, Parke-Davis 4. Tikkanen MJ, Helve E, Jäättelä A, et al. Comparison between lovastatin and gemfibrozil in the treatment of primary hypercholesterolemia: the Finnish Multicenter Study. Am J Cardiol. 1986:62:3514-31.

Please see last page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

Lopid® (Gemfibrozil Capsules and Tablets)

Before prescribing, please see full prescribing information. A Brief Summary follows

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS)

vity to gemfibrozil.

WARNINGS, 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated sub with clofibrate. There was no difference in mortality between the clofibrate-freated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-below texture was replications, and page capture. cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

buring the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statisticallysignificantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58%

greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). Gl malignancies and deaths from malignancies were not statistically

different between Lopid and placebo sub-groups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity

A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the genflibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically

from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been

demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should

4. Concomitant Anticoagulants - Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If

myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. Initial Therapy—Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every at tempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and

hypothyroidism that are contributing to the lipid abnormalities. Continued Therapy – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions**—(A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of gemitorozii and lovastatin therapy. It may be seen as early as 3 weeks airter initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANTS HOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIDER OF THE TO REPOWER THE REDUCE COMBINITATION.

THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. Carcinogenesis, Mutagenesis, Impairment of Fertility - Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

Lopid® (Gemfibrozil Capsules and Tablets)

from controls in the incidence of liver tumors, but the doses tested were lower than those

shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell

tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmit

5. Pregnancy Category B - Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 off-

spring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in

male and female rats, the use of Lopid in pregnancy should be reserved for those pa-tients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers** — Because of the potential for tumorigenicity shown for gem-fibrozii in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

 Hematologic Changes – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. Liver Function - Abnormal liver function tests have been observed occasionally

during Lopid administration, including eleva-tions of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist

 Use in Children – Safety and efficacy in children have not been established. ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in he Lopid group (placebo incidence in

(23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant differ ence between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%). **Gallbladder surgery** was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebial hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of musculoskeletal symptoms (See WARNINGS), and to abnormal liver function tests and hematologic changes (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were

more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treat-

by system: Measure and captured according to method according to m CAUSAL RELATIONSHIP PROBABLE: Gastrointestinal: cholestatic jaundice, Central Nervous System: dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; Eye: blurred vision; Genitourinary: impotence; Musculoskeletal: myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS): Clinical Laboratory: increased creatine phosphokinase, increased dirrubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; Hematopoietic: anemia, leukopenia, bone marrow hypoplasia, eosinophilia; Immunologic apoinedema, lavrogael edema, utilicaria, Integrammatary: exfoliative dermunologic: angioedema, laryngeal edema, urticaria; Integumentary: exfoliative der matitis, rash, dermatitis, pruritus.
CAUSAL RELATIONSHIP NOT ESTABLISHED: General: weight loss; Cardiac: extrasys

toles; Gastrointestinal: pancreatitis, hepatoma, colitis; Central Nervous System: confusion, convulsions, syncope; Eye: retinal edema; Genitourinary: decreased male fertility; Clinical Laboratory: positive antinuclear antibody; Hematopoietic: thrombocytopenia; Immunologic: anaphylaxis, Lupus-like syndrome, vasculitis; Integumentary: alopecia. DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary preven tion trial with gemfibrozil in middle-aged men with dyslipidemia. N Engl J Med 1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations an in the incidence of coronary heart disease in the Helsinki Heart Study. JAMA 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.): The Metabolic Basis of Inherited Disease, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.

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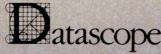
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## The American Journal of Cardiology

FEBRUARY 1, 1990, VOL. 65, NO. 5

### **CORONARY ARTERY DISEASE**

267

Frequency and Importance of Silent Myocardial Ischemia Identified with Ambulatory Electrocardiographic Monitoring in the Early In-Hospital Period After Acute Myocardial Infarction

Pamela Ouyang, Nisha Chibber Chandra, and Sidney O. Gottlieb

We studied the incidence of silent myocardial ischemia in 59 patients who had an uncomplicated early course after acute myocardial infarction. Silent ischemia occurs frequently very early after AMI and identifies a group of patients who are at increased risk for adverse in-hospital clinical outcomes.

### 271

Effects of Cigarette Smoking and Propranolol in Survivors of Acute Myocardial Infarction

Syed M. Jafri, Barbara C. Tilley, Robert Peters, Lonni R. Schultz, and Sidney Goldstein

The effect of propranolol on mortality and reinfarction was studied in relation to cigarette smoking habits in survivors of acute myocardial infarction. In survivors of AMI a beneficial effect of propranolol is observed, although cigarette smoking continues to be a risk factor for mortality after AMI even for those receiving propranolol.

### 277

Role of Previous Angina Pectoris and Collateral Flow to Preserve Left Ventricular Function in the Presence or Absence of Myocardial Infarction in Isolated Total Occlusion of the Left Anterior Descending Coronary Artery

Yves Juillière, Nicolas Danchin, Alain Grentzinger, Christine Suty-Selton, Jean P. Lethor, Thierry Courtalon, Claude Pernot, and François Cherrier

Do angina pectoris and collateral circulation influence myocardial function after isolated coronary occlusion? Using coronary angiography, we identified 58 patients with a complete isolated occlusion of the left anterior descending coronary artery. A longer duration of previous angina pectoris probably allows collateral development before coronary occlusion in 1-vessel coronary artery disease, thereby limiting myocardial damage.

### 282

Left Atrial Function in Acute Transient Left Ventricular Ischemia Produced During Percutaneous Transluminal Coronary Angioplasty of the Left Anterior Descending Coronary Artery

Ulrich Sigwart, Milan Grbic, Jean-Jacques Goy, and Lukas Kappenberger

We evaluated the left atrial function in 32 patients during percutaneous transluminal angioplasty of the left anterior descending artery. The hemodynamic values and contractility indexes demonstrate the important contribution of the left atrium to the filling of the ventricle and maintenance of cardiac function during ischemia.

### 28

Alcohol Consumption, Serum Lipids and Severity of Angiographically Determined Coronary Artery Disease Koichi Handa, Jun Sasaki, Keijiro Saku, Suminori Kono, and Kikuo Arakawa

We examined the relation of alcohol consumption to serum lipids and severity of coronary artery disease in a Japanese population of 212 men. Our findings suggest that moderate alcohol consumption may protect patients from severe coronary atherosclerosis.

### 290

Lack of Correlation Between Transient Myocardial Ischemia and Late Potentials on the Signal-Averaged Electrocardiogram

Gioia Turitto, Egidio Zanchi, Anna Lisa Risa, Angela Maddaluna, Mario Lucio Saltarocchi, Salvatore Fabio Vajola, and Pier Luigi Prati

To investigate the relation between transient myocardial ischemia and late potentials, serial signal-averaged electrocardiograms were performed in 100 patients with coronary artery disease before, during and after dipyridamole infusion. Electrophysiologic changes induced by transient myocardial ischemia may not have any relation with the substrate for chronic ventricular tachyarrhythmias, represented by late potentials on the signal-averaged electrocardiogram.

### 297

### Detection and Localization of Tumor Necrosis Factor in Human Atheroma

Peter Barath, Michael C. Fishbein, Jin Cao, James Berenson, Richard H. Helfant, and James S. Forrester

Is there a relation between tumor necrosis factor and the development of atherosclerosis? Using immunohistochemistry, we measured tumor necrosis factor in tissue sections; 88% of samples classified as atherosclerotic were positive for tumor necrosis factor while the factor was not present in normal arteries.

### 303

Quantitative Analysis of Amounts of Coronary Arterial Narrowing in Cocaine Addicts

Frederick A. Dressler, Sonya Malekzadeh, and William C. Roberts

Twenty-two cocaine addicts were studied at necropsy over a 10-year period and were divided into 2 groups: those with cocaine-related deaths and those in whom death was not due to cocaine. Our findings indicate that a large percentage of young cocaine addicts have significant coronary artery disease at necropsy.

### 309

### **Determinants of Hospital Charges for Coronary Artery Bypass Surgery: The Economic Consequences of Postoperative Complications**

George J. Taylor, Frank L. Mikell, H. Weston Moses, James T. Dove, Richard E. Katholi, Shezad A. Malik, Stephen J. Markwell, Cynthia Korsmeyer, Joel A. Schneider, and Harry A. Wellons

Data from 500 consecutive patients undergoing coronary artery bypass were analyzed according to preoperative variables and postoperative complications. No preoperative clinical feature emerged as a significant predictor of higher average charges; development of sternal wound infection, respiratory failure and left ventricular failure were associated with higher than average charges. Complications have a powerful influence on charges for coronary bypass, suggesting that programs with low average charges will have low complication rates.

### Attenuation of Exercise-Induced ST Depression During **Combined Isometric and Dynamic Exercise in Coronary Artery Disease**

Kim Bertagnoli, Peter Hanson, and Ann Ward

We measured ST-segment depression during submaximal dynamic and combined isometric-dynamic exercise testing in 11 men with stable coronary artery disease who were participating in an exercise training program. The results show that the rate-pressure product is not a valid index of ST response during isodynamic exercise in such patients.

### **ARRHYTHMIAS AND CONDUCTION DISTURBANCES**

### Relation of Syncope in Young Patients with Wolff-Parkinson-White Syndrome to Rapid Ventricular **Response During Atrial Fibrillation**

Thomas Paul, Paolo Guccione, and Arthur Garson, Jr.

Occurrence of atrial fibrillation with a rapid ventricular response over the accessory pathway during electrophysiologic study in 74 young patients ≤25 years old with Wolff-Parkinson-White syndrome provided high sensitivity and specificity to identify patients with a history of syncope. Electrophysiologic study may be helpful in identification of young patients with the WPW syndrome who are at risk of syncope.

### Value of Esophageal Pacing in Evaluation of Supraventricular Tachycardia

Béatrice Brembilla-Perrot, Frédéric Spatz, Ewad Khaldi, Arnaud Terrier de la Chaise, Diem Le Van, and Claude Pernot

To look for a sensitive stimulation protocol and for criteria to define the mechanism of reentry, we performed esophageal stimulation in 40 patients who had spontaneous paroxysmal supraventricular tachycardias. SVTs could be uniformly induced by programmed atrial stimulation in the control state and under isoproterenol; the location of the P wave in V1 compared to the ventriculogram and the esophageal electrocardiogram helped to define the mechanism of tachycardia.

### SYSTEMIC HYPERTENSION

### 331

### Comparison of Long-Term Hemodynamic Effects at Rest and During Exercise of Lisinopril Plus Sodium Restriction Versus Hydrochlorothiazide in Patients with **Essential Hypertension**

Per Omvik and Per Lund-Johansen

To investigate whether sodium restriction might replace thiazides in promoting blood pressure reduction by angiotensinconverting enzyme inhibitors, we compared the long-term hemodynamic effect of lisinopril plus sodium restriction versus lisinopril plus hydrochlorothiazide at rest and during exercise in 2 groups of essential hypertensive patients. Lisinopril plus low salt diet reduces the risk of unwanted metabolic effects and leads to more complete hemodynamic normalization than lisinopril plus diuretic and should be preferred when this leads to satisfactory BP control.

### **Effect of Postural Stimulation on Systemic Hemodynamics and Sympathetic Nervous Activity in Systemic Hypertension**

Joseph L. Izzo, Jr., Emilee Sander, and Patricia S. Larrabee

We studied 68 mildly hypertensive subjects and measured supine and upright plasma norepinephrine, blood pressure and cardiac output. Because plasma NE tends to be elevated in hypertension, cardiopulmonary baroreflexes may also be abnormal in this condition.

### **CONGESTIVE HEART FAILURE**

### Usefulness of Nicorandil in Congestive Heart Failure

Nazzareno Galiè, Elisabetta Varani, Luigi Maiello, Giuseppe Boriani, Stefano Boschi, Giorgio Binetti, and Bruno Magnani

Rest and exercise hemodynamic and hormonal effects of nicorandil, a nicotinamide-nitrate vasodilator, were assessed in 9 patients with New York Heart Association class II or III congestive heart failure and left ventricular ejection fraction ≤40%. Single oral doses of nicorandil in patients with CHF induced favorable changes on rest and exercise hemodynamics up to 6 to 8 hours, and an increase of renin activity was also observed.

### VALVULAR HEART DISEASE

### Follow-Up in Mitral Valve Prolapse by Phonocardiography, M-Mode and Two-Dimensional **Echocardiography and Doppler Echocardiography**

Deng You-Bing, Katsu Takenaka, Tsuguya Sakamoto, Yoshiyuki Hada, Jun-ichi Suzuki, Takahiro Shiota, Wataru Amano, Tsutomu Igarashi, Keiko Amano, Hisako Takahashi, and Tsuneaki Sugimoto

Follow-up phonocardiograms and echocardiograms were studied in 116 patients with mitral valve prolapse at an interval of 4.3 years (range 1 to 14 years). Although the degree of prolapse assessed by 2-dimensional echocardiography was unchanged, both phonocardiography and Doppler echocardiography showed an increase in the incidence of mitral regurgitation. M-mode echocardiography revealed increases in left atrial and ventricular sizes in patients with systolic murmur.

### In Vivo Identification of Mitral Valve Fibrosis and Calcium by Real-Time Quantitative Ultrasonic Analysis

Fabio Lattanzi, Eugenio Picano, Luigi Landini, Alessandro Mazzarisi, Gualtiero Pelosi, Antonio Benassi, Leonardo Salvatore, Alessandro Distante, and Antonio L'Abbate

Conventional echocardiography provides fundamental information about mitral valve morphology and function but has a relatively low specificity in evaluating valve calcific deposits, which is critical information for the preoperative decision to perform commisurotomy or replacement. We report on a microprocessor-based system for on-line evaluation of radiofrequency ultrasonic signals that can differentiate normal, fibrotic and calcific mitral valves in vivo.

### CARDIOMYOPATHY

### Angiographic and Electrophysiologic Substrates of Ventricular Tachycardia in Chronic Chagasic

Angelo A.V. de Paola, Leonard N. Horowitz, Mauro H. Miyamoto, Ronaldo Pinheiro, Dario F. Ferreira, Armenio B. Terzian, Claudio Cirenza, Nei Guiguer, Jr., Oscar P. Portugal, and Eulogio E. Martinez Fo

We describe the clinical, angiographic and electrophysiologic characteristics of 43 patients with ventricular tachycardia and chronic Chagasic myocarditis. Our data indicate that VT is frequently inducible in patients with sustained VT or nonsustained VT and chronic Chagasic myocarditis. There appears to be an association between conduction disturbances on the electrocardiogram and development of sustained arrhythmias.

### Regional Left Ventricular Wall Motion Abnormalities in **Dilated Idiopathic Cardiomyopathy**

Katharina Stibrant Sunnerhagen, Valmik Bhargava, and Ralph Shabetai

Regional wall motion was compared in 2 groups, 32 patients with idiopathic dilated cardiomyopathy and 17 control subjects, using a video technique that evaluates the whole cardiac cycle and provides information about systolic and diastolic events without assumptions regarding the left ventricle's position and orientation. Results suggest that basal wall motion is relatively preserved in dilated cardiomyopathy.

### **MISCELLANEOUS**

### Association of Echocardiographic Left Ventricular Mass with Body Size, Blood Pressure and Physical Activity (The Framingham Study) Daniel D. Savage, Daniel Levy, Andrew L. Dannenberg,

Robert J. Garrison, and William P. Castelli

We examined the relation between echocardiographically determined left ventricular mass and several clinical parameters in 4,972 Framingham Heart Study participants. Age, height, systolic blood pressure and body mass index emerged as significant, independent correlates of LV mass in both sexes; leisuretime physical activity was also associated with LV mass in men younger than 50.

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### Effect of Alteration in Loading Conditions on Both Normal and Abnormal Patterns of Left Ventricular Filling in Healthy Individuals

Thomas R. Downes, Abdel-Mohsen Nomeir, Kathy Stewart, Michael Mumma, Richard Kerensky, and William C. Little

We used Doppler echocardiography to examine left ventricular patterns in 3 different groups: normal subjects, elderly normal subjects and patients with left ventricular hypertrophy. We found that alterations of LV loading conditions alter the pattern of LV filling, regardless of the baseline value; however, simple changes in venous return do not "normalize" an abnormal pattern or vice versa.

### **METHODS**

### Accuracy of Digital Holter Monitoring of Extent and **Duration of Ischemic Episodes Compared to Analog**

Sigmund Silber, Ravi K. Bajaj, Katharine A. Kirk, and Gerald M. Pohost

We compared the usefulness of a digital, on-line, 2-channel Holter monitor to an analog amplitude-modulated recorder for ST-segment analysis. Identical leads were used (CM5 and CM<sub>3</sub>). The digital Holter device showed significantly better agreement and should be used to assess myocardial ischemia.

### **BRIEF REPORTS**

### 389

### **Mechanism of Directed Transluminal Atherectomy**

Danna E. Johnson, Lissa Braden, and John B. Simpson

### Reproducibility and Circadian Rhythm of Heart Rate Variability in Healthy Subjects

Heikki V. Huikuri, Kenneth M. Kessler, Elisabeth Terracall, Agustin Castellanos, Markku K. Linnaluoto, and Robert J. Myerburg

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### **Utility of a Stimulus Artifact Suppressor for Transesophageal Pacing**

D. Woodrow Benson Jr., Hossein Jadvar, and Janette F. Strasburger

### Lack of Sustained Hemodynamic Effects of the Beta<sub>2</sub>-Adrenoceptor Agonist Dopexamine in End-Stage **Congestive Heart Failure**

Michael Böhm, Elisabeth Reuschel-Janetschek, and Erland Erdmann

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### Leo Schamroth, A Tribute

Giuseppe Oreto

### **CASE REPORT**

### The Complex of Myxomas, Pigmentation and **Endocrine Overactivity**

Wesley S. Bennett, Thomas N. Skelton, and Patrick H. Lehan

### **INSTRUCTIONS TO AUTHORS on page A91**

### BALANCED CARDIODYNAMICS... THE LINK TO ANTIANGINAL **PROTECTION AND SAFETY**

CORONARY BLOOD FLOW

MYOCARDIAL CONTRACTION OF STATE OF STAT

HEART RATE

PERIPHERAL RESISTANCE

**BALANCED CARDIODYNAMICS ARE WHAT MAKE CARDIZEM** 

**TABLETS** 

Please see brief summary of prescribing information

on next page.

CARDIZEM\* (diltiazem HCI) is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

CAZAA659 058159

CARDIZ



Usual maintenance dosage: 180 to 360 mg/day



### MAKING THE DIFFERENCE IN ANGINA







60 mg

90 ma

120 ma

**BRIEF SUMMARY** 

CARDIZEM (diltiazem HCI) Tablets

### CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker,
(3) patients with hypotension (less than 90 mm Hg systolic),
(4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

- Cardiac Conduction. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or sec ond- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of dilfiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of
- 60 mg of diltiazem.

  Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
- Hypotension. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension
- Acute Hepatic Injury. In rare instances, significant eleva tions in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

### **PRECAUTIONS**

**General.** CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, labora-tory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired nal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with contin

ued dosing.

Dermatological events (see ADVERSE REACTIONS section)
may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when freating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly adminis-tered CARDIZEM to maintain optimum therapeutic blood

**Beta-blockers:** Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and betablockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunc

tion or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers re sulted in increased propranolol levels in all subjects and bio availability of propranolol was increased approximately 50% If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and dilliazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully mon-itored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24

healthy mole subjects increased plasma digoxin concentra-tions approximately 20%. Another investigator found no in-crease in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontin-uing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, con-ductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

**Pregnancy.** Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal  $\!\!\!\!/$ postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased inci-dence of stillbirths at doses of 20 times the human dose or

greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the poten-

tial benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted

Pediatric Use. Safety and effectiveness in children have not been established

### **ADVERSE REACTIONS**

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not

greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than

Cardiovascular: Angina, arrhythmia, AV block (first degree), AV block (second or third degree — see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.

Nervous System: Amnesia, depression, gait abnormality,

hallucinations, insomnia, nervousness, paresthesia, personality change, somno-lence, tinnitus, tremor.

Gastrointestinal: Ancrexia, constipation, diarrhea, dysgeu-sia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see

hepatic warnings), vomiting, weight increase

Petechiae, pruritus, photosensitivity, urti-Dermatologic:

Other:

Amblyopia, CPK elevation, dyspnea, epi staxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

Issued 11/88



CAZAA659

### The Heart Of Any Ultrasound System Is Its Transducers...

and COROMETRICS offers transducers to meet every cardiac application.

Our Aloka Color Flow Mapping System employs the most comprehensive array of transducers available today, including the 2.5 MHz, 3.5 MHz and 5.0 MHz high density imaging transducers...a 3.5 MHz dual function transducer for imaging, PW, CW, and high PRF Doppler...plus a 5.0 MHz small aperture short focus transducer. We currently offer the smallest diameter bi-directional transesophageal transducer available, and will soon have both bi-plane and pediatric transesophageal transducers. As your diagnostic requirements grow, Corometrics will continue to provide new transducers to serve your needs.

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Full range, real-tim dynamics focusin produces an extremel fine Ultrasound bean This allows the Alok 870 to maintain high frame rate wit no loss of image reso lution during the can diac study

### Corometrics support:

There is an added benefit built into your purchase of a new Aloka 870: Corometrics Medical Systems, Inc., the company that has service, applications, and educational resources to make the very most of your Ultrasound investment.

Before you buy any Ultrasound System, call us for a demonstration of the Aloka 870.





The Aloka 870.

For many hypertensive patients

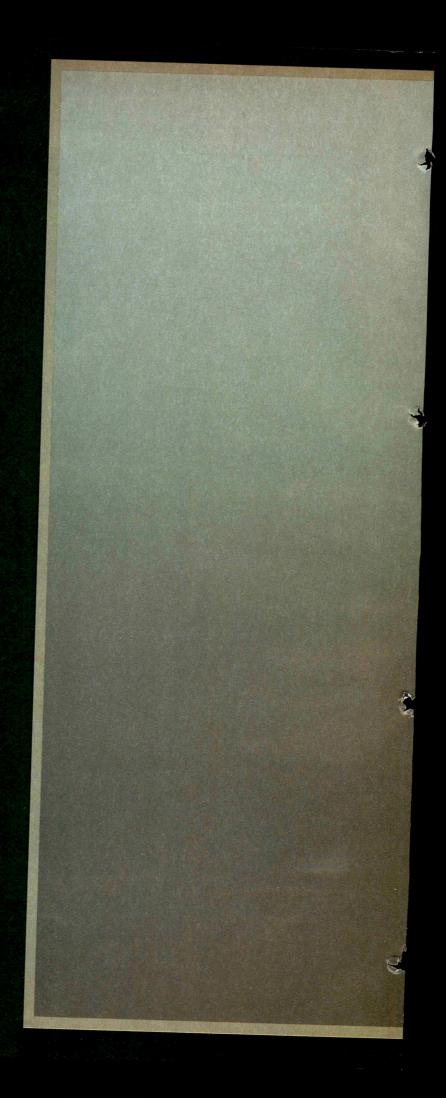
### THERAPY THAT MAY BE AS SILENT AS HYPERTENSION ITSELF

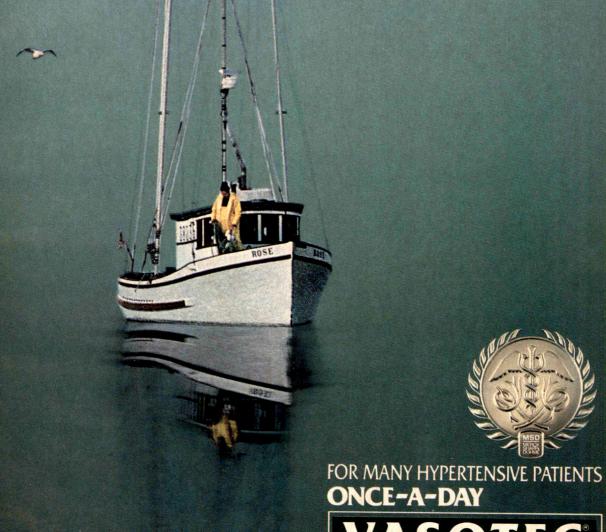
VASOTEC® (Enalapril Maleate, MSD) is generally well tolerated and not characterized by certain undesirable effects associated with selected agents in other antihypertensive classes.

VASOTEC is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

For a Brief Summary of Prescribing Information, please see the last page of this advertisement.

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(ENALAPRIL MALEATE MSD)





VASOTEC is available in 2.5-mg, 5-mg, 10-mg, and 20-mg tablet strengths.

Contraindications: VASOTEC\* (Enalaprii Maleate, MSD) is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Warnings: Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors; including VASOTEC, in such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful reclieving symptoms. Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered. (See ADVERSE REACTIONS)

REACTIONS.)

REACTIONS.

Phypotension: Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone, described with the properties of the p

Quitette may be inecessary.

\*\*Meutopenial Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially it they also have a collagen vascular disease Available data from clinical trials of enalignit are insufficient to show that enalignid does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalignit cannot be excluded. Periodic motioning of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: General: Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: Elevated serum potassium (>5.7 mEg/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See *Drug Interactions*). Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin Il formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and fold to report immediately any signs or symptoms suggesting angioedema (swell-ing of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure: patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutroperia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This informati is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse intended effects.

Drug Interactions:

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapri. The possibility of hypotensive effects with enalapri can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapri. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyl-dopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

adverse interactions.

Agents Increasing Serum Potassium: VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactione, triamterene, or amilioride), potassium supplements, potassium-containing sall substituties may lead to significant increases in serum potassium. Therefore, if concomiant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally in the used in patients with heart alluter receiving VASOTEC.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elim-ination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Pregnancy—Category C: There was no tetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day C50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters. There are no adequate and well-controlled studies of enalapril in pregnant women. However, data are available that

show enalapril crosses the human placenta. Because the risk of fetal toxicity with the use of ACE inhibitors has not been clearly defined. VASOTEC\* (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third frimesters of pregnancy has been associated with fetal and neonatal mor-bidity and mortality.

bidity and mortality. When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Inlants exposed in dero to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Problems associated with permaturity such as patent ductus arteriosis have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension, or the underlying prematurity.

Nursing Mothers: Milk in lactating rats contains radioactivity following administration of <sup>14</sup>C enalapril melate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

HYPERTENSION: The most frequent clinical adverse experiences in controlled trials were: headache (5.2%), dizziness (4.3%), and fatigue (3%).

(4.3%), and days (3.8%). Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%). HEART FAILURE. The most frequent clinical adverse experiences in both controlled and uncontrolled trials were dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), unrary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

erious clinical adverse experiences occurring since the drug was markeled or adverse experiences occurring to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each

Cardiovascular. Cardiac arrest. myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, *Hypotension*); cardiac arrest, pulmonary embolism and infarction; rhythm disturbances; atrial fibrillation; palpitation.

Digestive: Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, dyspepsia, constipation, glossitis, stomatitis.

Musculoskeletal: Muscle cramps.

Nervous/Psychiatric. Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Urogenital: Renal failure, oliguria, renal dystunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). Respiratory: Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection.

Skin: Herpes zoster, urticaria, pruritus, alopecia, flushing, hyperhidrosis.

Special Senses: Blurred vision, taste alteration, tinnitus.

A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgias/arthritis, myalgias, lever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash, and other dermatologic manifestations.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be tatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treat-ment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS)

The transfer of Should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

Clinical Laboratory Test Findings

Gerum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS). hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or patients with real artery stenosis. (See PRECAUTIONS.) In patients with seart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine. usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hemoglobin and Hematocrit. Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 0% and 10 v01%, respectively) occur frequently in either hypertension or heat failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 01% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutronenia, thrombocytonenia, and

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported. A few cases of hemolysis have been reported in patients with G6PD

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred

Dosage and Administration: Hypertension: In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed. If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS. Drug Interactions.)

Thorse, Drug Interactions.)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in Na divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of I dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blo pressure is not controlled with VASOTEC alone, a diuretic may be added.

possing interval. In SIGN patents, an interease in closure of the pressure is not controlled with VASOTEC alone, a disretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing disretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Hypertensive Patients with Renal Impairment: The usual dose of enalapril is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance > 30 mL/min (serum creatinine > 3 mg/dL). For patients with creatinine clearance > 30 mL/min (serum creatinine > 3 mg/dL). For patients with creating clearance > 30 mL/min (serum creatinine) and the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily. The dosage may be titrated upward until blood pressure has stabilized for at least an additional hour. (See WARN-INSS and PRECAUTIONS, Drug Interactions). If possible, the dose of the district is a district of the district o

may be adjusted opening upon clinical or lientury with the art failure and Benal Impairment or Hyponatremia. In patients with Heart Failure and Benal Impairment or Hyponatremia. In patients with heart failure who have hyponatremia (serum sodium < 130 mEq/L) or with serum creatinine > 1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION. Heart Failure, WARNINGS, and PRECAUTIONS, Drug Interactions.) The dose may be increased to 2.5 mg bi.d. then 5 mg bi.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

For more detailed information, consult your MSD Representative or see Prescribing Information, Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486. J9VS54RIBBB



CONTENTS/ABSTRACTS

FEBRUARY 1, 1990, VOL. 65, NO. 5

## The American Journal of Cardiology

### **CORONARY ARTERY DISEASE**

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Frequency and Importance of Silent Myocardial Ischemia Identified with Ambulatory Electrocardiographic Monitoring in the Early In-Hospital Period After Acute Myocardial Infarction Pamela Ouyang, Nisha Chibber Chandra, and Sidney O. Gottlieb

We studied the incidence of silent myocardial ischemia in 59 patients who had an uncomplicated early course after acute myocardial infarction (AMI). Calibrated 2-lead ambulatory electrocardiographic monitoring performed for  $39 \pm 2$  hours starting  $4 \pm 1$  days after AMI identified silent myocardial ischemia ( $\geq 1$  mm ST-segment change lasting  $\geq 2$  minutes) in 27 patients. These patients had  $5 \pm 1$  episodes lasting a median of 11 minutes/episode (range 2 to 36 minutes/episode). There was no difference in clinical characteristics, antiischemic medications or severity of coronary disease by angiography between patients with or without silent ischemia. Fourteen of 27 patients (52%) with silent ischemia had  $\geq 1$  inhospital clinical ischemic event (pulmonary edema, n = 5, cardiac death, n = 1, or postinfarction angina, n = 11). However, only 7 of 32 patients without silent ischemia (22%) had  $\geq 1$  in-hospital event (pulmonary edema, n = 1, cardiac death, n = 1, postinfarction angina, n = 6) (p < 0.02 compared to patients with silent ischemia).

### 271

### Effects of Cigarette Smoking and Propranolol in Survivors of Acute Myocardial Infarction

Syed M. Jafri, Barbara C. Tilley, Robert Peters, Lonni R. Schultz, and Sidney Goldstein

The effect of propranolol on mortality and reinfarction was studied in relation to cigarette smoking habits in survivors of acute myocardial infarction (AMI). Among cigarette smokers (n=2,332), the placebo group had higher mortality than the propranolol group (11 vs 7.4%, p <0.0008) and more sudden coronary deaths (7.1 vs 4.6%, p <0.009). In nonsmokers, the placebo group had a slightly higher mortality (7.5 vs 7.1%, p >0.64) than the propranolol group. After adjusting for baseline differences, both treatment with propranolol and nonsmoking were predictors of survival. In survivors of AMI, a beneficial effect is observed for cigarette smokers.

Role of Previous Angina Pectoris and Collateral Flow to Preserve Left Ventricular Function in the Presence or Absence of Myocardial Infarction in Isolated Total Occlusion of the Left **Anterior Descending Coronary Artery** 

Yves Juillière, Nicolas Danchin, Alain Grentzinger, Christine Suty-Selton, Jean P. Lethor, Thierry Courtaion, Claude Pernot, and François Cherrier

Coronary angiography diagnosed 58 patients with a complete isolated occlusion of the left anterior descending coronary artery. Duration of previous angina pectoris was defined and compared to the left ventricular ejection fraction and the development of collateral circulation. The group of 40 patients with "well-developed" collaterals had the higher ejection fraction and the longer duration of previous angina pectoris. A longer duration of previous angina pectoris probably allowed collateral development before coronary occlusion in 1-vessel coronary artery disease, thereby limiting myocardial damage.

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Left Atrial Function in Acute Transient Left Ventricular Ischemia Produced During Percutaneous Transluminal Coronary Angioplasty of the Left Anterior Descending **Coronary Artery** 

Ulrich Sigwart, Milan Grbic, Jean-Jacques Goy, and Lukas Kappenberger

We evaluated the left atrial function in 32 patients during percutaneous transluminal angioplasty of the left anterior descending artery. The hemodynamic values and contractility indexes demonstrate the important contribution of the left atrium to the filling of the ventricle and maintenance of cardiac function during ischemia.

287

Alcohol Consumption, Serum Lipids and Severity of **Angiographically Determined Coronary Artery Disease** 

Koichi Handa, Jun Sasaki, Keijiro Saku, Suminori Kono, and Kikuo Arakawa

The relation of alcohol consumption to serum lipids and severity of coronary artery disease was examined. Alcohol consumption was positively associated with high-density lipoprotein cholesterol and inversely associated with total cholesterol, but was not associated with triglyceride. After adjustment for these serum lipids as well as for cigarette smoking and systemic hypertension, the risk of coronary stenosis was significantly decreased in the moderate drinkers (101 to 300 ml alcohol/week). A decreased risk among moderate drinkers also was noted in terms of Gensini's severity score. These findings suggest that moderate alcohol consumption may protect against severe coronary atherosclerosis.

Continued on page A23

### THE INSIDE STORY

**Effective** peripheral vasodilation<sup>1</sup> **Undiminished** Undiminished cardiac output<sup>2</sup>

renal function<sup>3-5</sup>









### TRANDATE bid labetalol HCl/100 mg tablets Because it vasodilates

Allen & Hanburys

References: 1. Lund-Johansen P. Short- and long-term (six-year) hemodynamic effects of labetalol in essential hypertension. *Am J Med* 1983:75(suppl 4A):24-31. 2. Koch G: Haemodynamic adaptation at rest and during exercise to long-term antihypertensive treatment with combined alpha- and beta-adrenoreceptor biockade by labetalol. *Br Heart J* 1979:41(2):192-198. 3. Wallin JD: Antihypertensives and their impact on renal function. *Am J Med* 1983:75(suppl 4A):103-108. 4. Pedersen EB. Larsen JS: Effect of propranolol and labetalol on renal haemodynamics at rest and during exercise in essential hypertension. *Postgrad Med J* 1980;56(suppl 2):27-32. 5. Malini PL. Strocchi E. Negroni S. et al: Renal haemodynamics after chronic treatment with labetalol and propranolol. *Br J Clin Pharmacol* 1982;13(suppl 1):123S-126S.

BRIFF SUMMARY

(labetalol hydrochloride)

The following is a brief summary only. Before prescribing, see complete prescribing information in Trandate\* Tablets product labeling.

CONTRAINDICATIONS: Trandate\* Tablets are contraindicated in bronchial asthma, overt cardiac fail-

reater-than-first-degree heart block, cardiogenic shock, and severe bradycardia (see WARN

WARNINGS: Hepatic Injury: Severe hepatocellular injury, confirmed by rechallenge in at least one case, occurs rarely with labetalol therapy. The hepatic injury is usually reversible, but hepatic necrosis and death have been reported. Injury has occurred after both short- and long-term treatment and may be slowly progressive despite minimal symptomatology. Appropriate laboratory testing should be done at the first symptom/sign of liver dysfunction (eg. pruritus, dark urine, persistent anorexia, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms). If the patient has laboratory acidence of their injury or jaundice, labetalol should be stonged and not restarted. jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms). If the patient has laboratory evidence of liver injury or jaundice, labetalol should be stopped and not restarted.

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta-blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response should be observed closely. If cardiac failure continues despite adequate digitalization and diuretic, Trandate\* therapy should be withdrawn (expectable). (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy, exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. When discontinuing chronically administered Trandate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Trandate carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Irandate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease sommon and may be unrecognized, it may be prudent not to discontinue Trandate therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g. Chronic Bronchitis and Emphysema): Patients with bronchospastic disease should, in general, not receive beta-blockers. Trandate may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if

andate is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous

Pheochromocytoma: Labetalol HCl has been shown to be effective in lowering blood pressure and

Pheochromocytoma: Labetalol HGI has been shown to be effective in lowering blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HGI to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg. tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; thay therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy before major surgery is controversial. Protracted seyers hypogension and difficulty in restarting or maintaining a

gery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see PRECAUTIONS:

PRECAUTIONS: General: Impaired Hepatic Function: Trandate\* Tablets should be used with caution In patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction: (see WARNINGS).

Information for Patients: As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incidence of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl. dosing with Trandate Tablets should not be interrupted or discontinued without a physicaln's advice. Patients being treated with Trandate Tablets should consult a physician at any signs or symptoms of impending cardiac failure or hepatic dysfunction (see WARNINGS). Also, transient calp tingling may occur, usually when treatment with Trandate Tablets is initiated (see ADVERSE

Laboratory Tests: As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions: In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a

drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal antiasthmatic

dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCI. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCI. special care should be used in establishing the dose required for blood pressure control in such natients

nergism has been shown between halothane anesthesia and intravenously administered labetalol HCI. During controlled hypotensive anesthesia using labetalol HCI in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving

Labetalol HCI blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

### Trandate® (labetalol hydrochloride) Tablets

Drug/Laboratory Test Interactions: The presence of labetalol metabolites in the urine may result in falsely elevated levels of urinary catecholamines, metanephrine, normetanephrine, and vanillylman-delic acid when measured by fluorimetric or photometric methods. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCI, a specific method, such as a high

naving a pheconformocytoma and being treated with laderation Hot, a specific intention, such as a high performance liquid chromatographic assay with solid phase extraction (eg., *J Chromatogr* 385: 241.1987) should be employed in determining levels of catecholamines.

Labetalol HCl has also been reported to produce a false-positive test for amphetamine when screening urine for the presence of drugs using the commercially available assay methods Toxi-Lab A\* (thin-layer chromatographic assay) and Emit-d. a. u. \* (radioenzymatic assay). When patients being treated with labetalol have a positive urine test for amphetamine using these techniques, confirmation should be made by using more specific methods, such as a gas chromatographic-mass spectrometer

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCI for 18 months in mice and for two years in rats showed no evidence of carcinogenesis. Studies with labetalol HCI using dominant lethal assays in rats and mice and exposing microorganisms according to modified Ames tests showed no evidence of mutagenesis.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Teratogenic studies were performed with labetalol in rats and rabbits at oral doses up to approximately six and four times the maximum rec mended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was mended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. A teratology study performed with labetalol in rabbits at intravenous doses up to 1.7 times the MRHD revealed no evidence of drug-related harm to the fetus. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

\*\*Nonteratogenic Effects:\*\* Transient hypotension, bradycardia, and hypoglycemia have been rarely observed in infants of mothers who were treated with labetalol HCl for hypertension during pregnancy. Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHD caused a decrease in neonatal survival.

\*\*Labor and Delivery:\*\* Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when Trandate Tablets are administered to a nursing woman

Pediatric Use: Safety and effectiveness in children have not been established

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects are mild and transient and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, discontinuation of Trandate® Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8% to 10% of patients, and a centrally acting alpha-agonist led to discontinuation in 30% of patients.

The following adverse reactions were derived from multicenter, controlled clinical trials over treatment periods of three and four months. The rates, which ranged from less than 1% to 5% except as otherwise noted are based on adverse reactions, considered prohably drug-related by the investiga-

otherwise noted, are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (eg, dizziness, 20%; nausea, 14%

Body as a Whole: Fatigue, asthenia, headache. Gastrointestinal: Nausea (6%), vomiting, dyspepisa, diarrhea, taste distortion. Central and Peripheral Nervous Systems: Dizziness (11%), paresthesia, drowsiness. Autonomic Nervous System: Nasal stuffiness, ejaculation failure, impotence, increased sweating. Cardiovascular: Edema, postural hypotension. Respiratory: Dyspnea.

Skin: Rash. Special Senses: Vision abnormality, vertigo.

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, ie, a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contra-

indications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2,400 mg in more severely hypertensive patients. The US therapeutic trials data base for adverse reactions that are clearly or possibly dose-related shows that the following side effects increased with increasing dose: dizziness, fatigue, nausea, vomiting, dyspepsia, paresthesia, nasal stuffiness, ejaculation failure, impotence, and

In addition, a number of other less common adverse events have been reported

Body as a Whole: Fever. Cardiovascular: Postural hypotension, including, rarely, syncope. Central and Peripheral Nervous Systems: Paresthesia, most frequently described as scalp tingling. In most cases, it was mild and transient and usually occurred at the beginning of treatment. Collagen Disorders: Systemic lupus erythematosus, positive antinuclear factor. Eyes: Dry eyes. Immunological System: Antimitochondrial antibodies. Liver and Biliary System: Hepatic necrosis, hepatitis, chole System: Antimitochondrial antibodies. Liver and Biliary System: Hepatic necrosis, hepatitis, cholestatic jaundice, elevated liver function tests. Musculoskeletal System: Muscle cramps, toxic myopathy. Respiratory System: Bronchospasm. Skin and Appendages: Rashes of various types, such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriaform, and facial erythema; Peyronie's disease; reversible alopecia. Urinary System: Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects: In addition, other adverse effects not listed above have been reported with other heta-adreneroic blocking agents. Central Nervous System: Reversible mental depression pro-

other beta-adrenergic blocking agents. Central Mervous System: Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on psychometrics. Cardiovascular: Intensification of A-V block (see CONTRAINDICA-TIONS). Allergic: Fever combined with aching and sore throat, laryngospasm, respiratory distress. Hemalologic: Agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura. Gastrointestinal: Mesenteric artery thrombosis, ischemic collitis. The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCI.

Clinical Laboratory Tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested and, more rarely, reversible increases in blood urea.

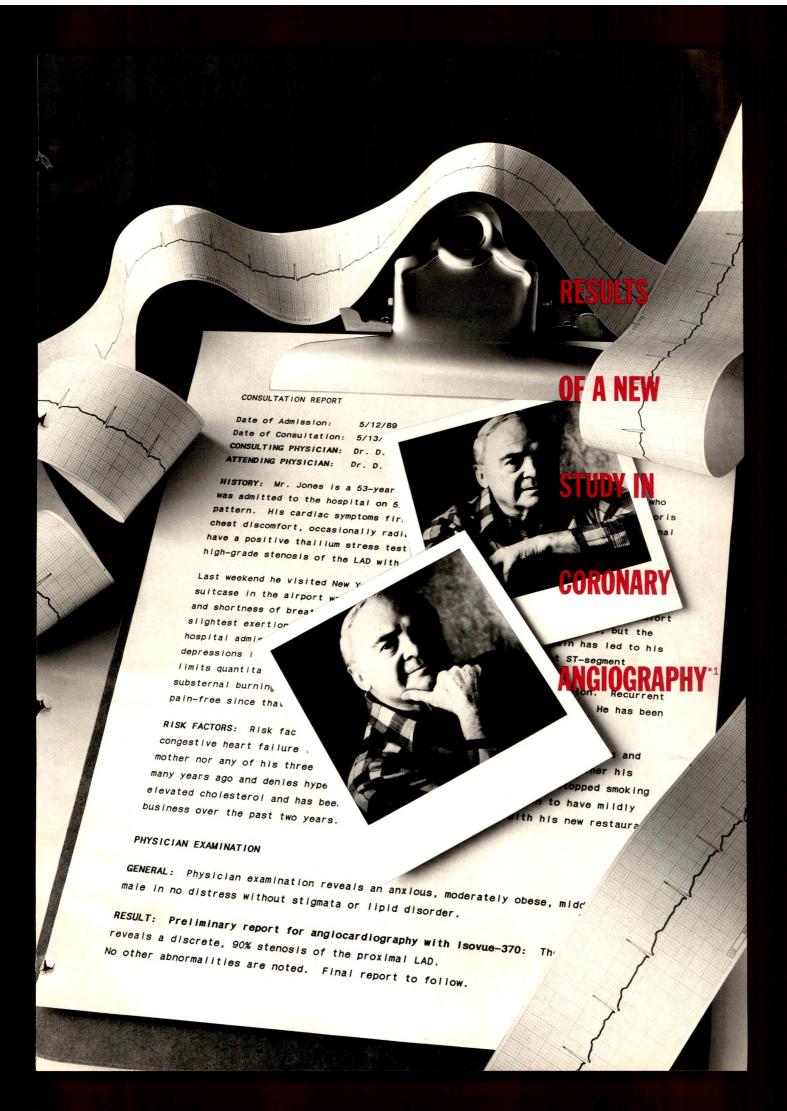
OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full pre-

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. The recommended initial dosage is 100 mg twice daily whether used alone or added to a diuretic regimen. After two or three days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every two or three days. The usual maintenance dosage of labetalol HCl is between 200 and 400 mg twice daily. Before use, see complete prescribing information for dosage details

August 1989



DIVISION OF GLAXO INC. Research Triangle Park, NC 27709



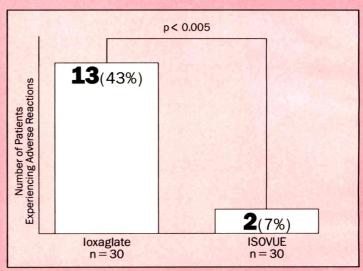
**CLASSIC IMAGES** 

**WITH A LOWER** 

**INCIDENCE OF** 

**ADVERSE REACTIONS** 

Nonionic ISOVUE-370 (iopamidol injection 76%) Exhibits Lower Incidence of Adverse Reactions than Ionic Ioxaglate



The number of patients experiencing adverse reactions was significantly less with ISOVUE than with ioxaglate.

These results indicate that the nonionic contrast medium iopamidol is better tolerated than the ionic dimer ioxaglate during cardiac and coronary angiography.

\*A double-blind study involving 60 male patients (30 patients in each group) was conducted to compare the electrocardiographic and hemodynamic effects of ISOVUE and ioxaglate. Procedures studied were left ventriculography and selective coronary angiography. There were no statistical differences in age, severity of coronary artery disease, or LV function between each group.

<sup>1</sup> Wisneski JA, Gertz EW, Dahlgren M, Muslin A: Comparison of low osmolality ionic (loxaglate) versus nonionic (lopamidol) contrast media in cardiac angiography. Am J Cardiol 1989; 63:487-495.

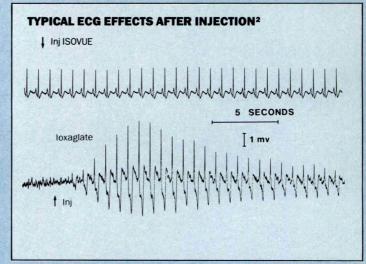
**CLASSIC IMAGES** 

**WITH A LOWER** 

**INCIDENCE OF** 

**ECG CHANGES** 

Nonionic ISOVUE-370 (iopamidol injection 76%) Exhibits Less Impact on the Myocardium than Ionic loxaglate



Compared to ioxaglate, ISOVUE had no significant ECG effects during right coronary angiography.

This report demonstrates that mild to moderate adverse reactions, QT interval prolongations, ST and T wave changes are significantly greater during coronary angiography with ioxaglate compared with iopamidol. 99<sup>1</sup>

P 3-5,454

As with all injectable contrast agents, the possibility of severe reactions should be borne in mind, regardless of patient's preexisting medical history.

<sup>2</sup> Data on file, Squibb Institute for Medical Research.

See following page for brief summary of prescribing information.

NONIONIC

(iopamidol injection 76%)

The Molecule Makes the Difference



ISOVUE\*-200 lopamidol Injection 41%

ISOVUE\*-300 lopamidol Injection 61%

ISOVUE\*-370 lopamidol Injection 76%

### CONTRAINDICATIONS-None.

**WARNINGS**—Nonionic iodinated contrast media inhibit blood coagulation, *in vitro*, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state, and concomitant medications may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended including close attention to guidewire and catheter manipulation, use of manifold systems and/or three way stopcocks, frequent catheter flushing with heparinized saline solutions, and minimizing the length of the procedure. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of in vitra clotting.

syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of *in vitro* clotting.

Use caution in patients with severely impaired renal function, combined renal and hepatic disease, or anuria, particularly when larger doses are administered. Radiopaque diagnostic contrast agents are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly in those with therapeutically resistant anuria. It has been speculated that the combination of the contrast agent and dehydration may be causative of anuria in myelomatous patients. This risk is not a contraindication; however, special precautions are required. Contrast media may promote sickling in individuals who are homozygous for sickle cell disease when injected intravenously or intraverarterially. Administration to patients known or suspected of having pheochromocytoma should be performed with extreme caution. If the possible benefits outweigh the considered risks, the procedures may be performed; however, the amount of the mediunjected should be kept to an absolute minimum. Assess blood pressure throughout the procedure and have measures for treatment of a hypertensive crisis available. Monitor such patients very closely. Use caution in patients with hyperthyroidism or with an autonomously functioning thyroid nodule because of risk of thyroid storm.

PRECAUTIONS: General—Diagnostic procedures should be carried out under the direction of personnel with the prerequisite training and a thorough knowledge of the particular procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, or for emergency treatment of severe reaction to the agent itself. After parenteral administration, competent personnel and emergency facilities should be available for at least 30 to 60 minutes since severe delayed reactions may occur. Preparatory dehydration is dangerous and may contribute to acute renal failure in susceptible patients. Patients should be well hydrated prior to and following administration. Reactions to the medium, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions, should always be considered (see ADVERSE REACTIONS in the product package insert). Patients at increased risk include those with a history of a previous reaction to a contrast medium, a known sensitivity to iodine per se, and a known clinical hypersensitivity (bronchial asthma, hay fever, and food alergies). Pretesting cannot be relied upon to predict severe reactions and may itself be hazardous for the patient. A thorough medical history with emphasis on allergy and hypersensitivity prior to the injection of any contrast medium may be more predictive and accurate than pretesting. Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered. General anesthesia may be indicated in some procedures in selected patients; however, a higher incidence of adverse reactions has been reported in anesthetized patients, which may be attributable to the inability of the patient to identify untoward symptoms, or to the hypotensive effect of anesthesia which can reduce cardiac output and increase the duration of exposure to the agent. Even though the osmolality is low compared to distodying plaques or damaging or perforation to be sweet all durin

The inhibitory effects of nonionic contrast media on mechanisms of hemostasis have been shown, in vitro, to be less than ionic contrast media at comparable concentrations. For this reason, standard angiographic procedures should always be followed: angiographic catheters should be flushed frequently, and prolonged contact of blood with contrast in syringes and catheters should be avoided. Perform selective coronary arteriography only in those in whom the expected benefits outweigh the procedural risk. The inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure. Angiography should be avoided whenever possible in patients with homocystinuria, because of the risk of inducing thrombosis and embolism.

In addition to the general precautions previously described, special care is required when venography is performed in patients with suspected thrombosis, phlebitis, severe ischemic disease, local infection or a totally obstructed venous system.

Extreme caution during injection of contrast media is necessary to avoid extravasation and fluoroscopy is recommended. This is especially important in patients with severe arterial or venous disease.

**Drug Interactions**—Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by intravascular contrast agents. Administration of intravascular agents should therefore be postponed in any patient with a known or suspected hepatic or biliary disorder who has recently received a cholecystographic contrast agent. Other drugs should not be admixed with iopamidol.

Drug/Laboratory Test Interactions—PBI and radioactive iodine uptake studies will not accurately reflect thyroid function for up to 16 days following administration, however T3 resin uptake and total or free thyroxine (T4) assays are not affected. Any test which might be affected by contrast media should be performed prior to administration of the

Carcinogenesis, Mutagenesis, Impairment of Fertility—In animal reproduction studies performed on rats, intravenously administered iopamidol did not induce adverse effects on fertility or general reproductive performance. In studies to determine mutagenic activity, iopamidol did not cause any increase in mutation rates.

Pregnancy Category B—No teratogenic effects attributable to iopamidol have been observed in teratology studies performed in animals. There are, however, no adequate and well controlled studies in pregnant women. It is not known whether iopamidol crosses the placental barrier or reaches fetal tissues. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Radiologic procedures involve a certain risk related to the exposure of the fetus to ionizing radiation.

**Labor and Delivery**—It is not known whether use during labor or delivery has immediate or delayed adverse effects on the labor, the delivery or the newborn.

Nursing Mothers—It is not known whether iopamidol is excreted in human milk. Use caution when contrast media are administered to nursing women because of potential adverse reactions; consideration should be given to temporarily discontinuing nursing.

Pediatric Use—Safety and effectiveness in children has been established in pediatric angiocardiography.

angiocardiography.

Pediatric patients at higher risk of experiencing adverse events during contrast medium administration may include those having asthma, a sensitivity to medication and/or allergens, cyanotic heart disease, congestive heart failure, a serum creatinine greater than 1.5 mg/dL or those less than 12 months of age.

ADVERSE REACTIONS—Usually mild to moderate, self-limited and transient. In angiocardiography (597 patients), the adverse reactions with an estimated incidence of one percent or higher are: hot flashes 3.4%; angina pectoris 3.0%; flushing 1.8%; bradycardia 1.3%; hypotension 1.0%; hives 1.0%. Intravascular injection is frequently associated with the sensation of warmth and pain, especially in peripheral arteriography and venography; pain and warmth are less frequent and less severe with ISOVUE (inpamidol injection) than with diatrizoate meglumine and diatrizoate sodium injection. The following table of incidence of reactions is based on clinical studies with ISOVUE in about 1941 patients.

### **Adverse Reactions**

Estimated Overall Incidence				
System	> 1%	≤ 1%		
Cardiovascular	none	tachycardia hypotension hypertension myocardial ischemia circulatory collapse S-T segment depression bigeminy extrasystoles ventricular fibrillation angina pectoris bradycardia transient ischemic attack thrombophlebitis		
Nervous	pain (2.8%) burning sensation (1.4%)	vasovagal reaction tingling in arms grimace faintness		
Digestive	nausea (1.2%)	vomiting anorexia		
Respiratory	none	throat constriction dyspnea pulmonary edema		
Skin and Appendages	none	rash urticaria pruritus flushing		
Body as a Whole	hot flashes (1.5%)	headache fever chills excessive sweating back spasm		
Special Senses	warmth (1.1%)	taste alterations warmth in throat/arms/chest nasal congestion visual disturbances		
Urogenital	none	urinary retention		

Regardless of the agent employed, overall estimated incidence of serious adverse reactions is higher with coronary arteriography than with other procedures. Cardiac decompensation, serious arrhythmias, or myocardial ischemia or infarction may occur during coronary arteriography and left ventriculography. Following coronary and ventricular injections, certain electrocardiographic changes (increased QTc, increased R-R, T-wave amplitude) and certain hemodynamic changes (decreased systolic pressure) occurred less frequently with ISOVUE (iopamidol injection) than with diatrizoate meglumine and diatrizoate sodium injection; increased LVEDP occurred less frequently after ventricular iopamidol injections. In aortography, the risks of procedures also including infarction and acute tubular necrosis with oliguria and anuria, accidental selective filling of the right renal artery during the translumbar procedure in the presence of pre-existing renal disease, retroperitoneal hemorrhage from the translumbar approach, and spinal cord injury and pathology associated with the syndrome of transverse myelitis. Adverse effects reported in literature include arrhythmia, arterial spasms, hematuria, perioribital edema, involuntary leg movement, malaise, and triggering of deglutition; some of these may be procedural. Other reactions due to procedural hazards include hemorrhage or pseudoaneurysms at the puncture site, brachial plexus palsy following axillary artery injections, chest pain, myocardial infarction, and transient changes in hepatorenal chemistry tests; and rarely arterial thrombosis, displacement of arterial plaques, venous thrombosis, dissection of the coronary vessels and transient sinus arrest.

General Adverse Reactions To Contrast Media—Reactions known to occur with parenteral administration of iodinated ionic contrast agents (see the listing below) are possible with any nonionic agent. Life-threatening reactions and fatalities, mostly of cardiovascular origin, have occurred. Reported incidences of death from the administration of other iodinated contrast media range from 6.6 per 1 million (0.00066%) to 1 in 10,000 patients (0.01%). Most deaths occur during injection or 5 to 10 minutes later, the main feature being cardiac arrest with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock (est. 0.005%) are found in the literature. Experience with iopamidol suggests there is much less discomfort (e.g., pain and/or warmth) with peripheral arteriography. Fewer changes are noted in ventricular function after ventriculography and coronary arteriography. The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that for the general population, patients with a history of previous reactions to a contrast medium are three times more susceptible. Most reactions to intravascular contrast agents appear within 1-3 minutes after the start of injection, but delayed reactions may occur (see PRECAUTIONS, General). Adverse reactions reported with other intravascular contrast agents and theoretically possible with iopamidol include: Cardiovascular: vasodilation, cerebral hematomas, petechiae; Nervous: paresthesia, dizziness, convulsions, paralysis, coma; Respiratory: increased cough, asthma, laryngeal edema, pulmonary edema, bronchospasm, rhinitis; Skin and Appendages: injection site pain usually due to extravasation and/or erythematous swelling, skin necrosis; Urogenital: osmotic nephrosis of proximal tubular cells, renal failure, pain; Special Senses: bilateral ocular irritation; lacrimation; conjunctival chemosis, infection, and conjunctivitis; Other: neutropenia, thrombophlebitis, flushing, pallor, weakness, severe

For full prescribing information consult package insert.

(J3-652H

Under license from Bracco Industria Chimica S.p.A. U.S. Patent #4,001,323

### Lack of Correlation Between Transient Myocardial Ischemia and Late Potentials on the Signal-Averaged Electrocardiogram

Gioia Turitto, Egidio Zanchi, Anna Lisa Risa, Angela Maddaluna, Mario Lucio Saltarocchi, Salvatore Fabio Vajola, and Pier Luigi Prati

To investigate the relation between transient myocardial ischemia and late potentials, serial signal-averaged electrocardiograms were performed in 100 patients with coronary artery disease before, during and after dipyridamole infusion. During this test, 47 patients (group 1) developed transient myocardial ischemia (with ST elevation in 14 and ST depression in 33), while 53 patients (group 2) did not. Baseline recordings were abnormal in 20 cases (20%), with no significant differences between groups 1 and 2 (26 and 15%, respectively). In both groups, no significant changes were noted on signal-averaged electrocardiograms recorded before, during and after the test. During the test, 100% of abnormal baseline recordings remained abnormal and 98% of normal recordings remained normal. In 2 cases only from group 1, the signal-averaged electrocardiogram had borderline values at baseline and became transiently abnormal during dipyridamoleinduced ischemia. Thus, electrophysiologic changes induced by transient myocardial ischemia may not have any relation with the substrate for chronic ventricular tachyarrhythmias, represented by late potentials on the signal-averaged electrocardiogram.

### 297

### **Detection and Localization of Tumor Necrosis Factor in Human Atheroma**

Peter Barath, Michael C. Fishbein, Jin Cao, James Berenson, Richard H. Helfant, and James S. Forrester

We demonstrated the presence of tumor necrosis factor (TNF) with immunohistochemistry in 88% of human arteries with significant atherosclerosis and in 65% of arteries with intimal thickening. There was no TNF present in normal arteries. Immunoreactive TNF was localized in the cytoplasm of macrophages and in the cytoplasm or on the membrane of vascular smooth muscle cells and endothelial cells.

### 303

### **Quantitative Analysis of Amounts of Coronary Arterial Narrowing in Cocaine Addicts**

Frederick A. Dressler, Sonya Malekzadeh, and William C. Roberts

From January 1979 to February 1989, we studied at necropsy 22 cocaine addicts. The 22 patients were divided into 2 groups: death due to cocaine overdose (13 patients, aged 23 to 45 years [mean 32], and mean total blood cocaine level, 0.36 mg/dl) and noncocaine-related death (9 patients, aged 15 to 50 years [mean 32]). Of the 22 patients, 17 were men and 5 were women; 19 were black and 3 were white. Gross examination in the 22 patients disclosed that 8 patients (36%) had 1 or more of the 4 major (left main, left anterior descending, left circumflex and right) coronary arteries

narrowed at some point >75% in cross-sectional area by atherosclerotic plaque. In 17 cases, the 4 major epicardial coronary arteries were divided into 805 five-mm long segments and a histologic section was prepared from each segment: of the 12 patients with toxic blood concentrations of cocaine at necropsy, 41 (8%) of 544 five-mm coronary segments were narrowed 76 to 100% and 106 segments (19%) were narrowed 51 to 75% in cross-sectional area by plaque. Of the 5 cocaine addicts in whom death was not related to cocaine use, 8 (3%) of 261 five-mm coronary segments were narrowed 76 to 100% and 19 segments (7%) were narrowed 51 to 75% in cross-sectional area by plaque. These findings suggest that the frequency of coronary artery narrowing is greater in patients who die shortly after taking cocaine compared to those with death not due to cocaine overdose. The frequency of severe coronary arterial narrowing is considerably greater than expected for the entire group of patients whose mean age was only 32 years. Thus, either of 2 possibilities, alone or in combination, may explain our findings: coronary atherosclerosis is accelerated by cocaine addiction for reasons as yet undetermined, or cocaine provides a fatal stress in patients with premature atherosclerosis from other causes.

### 309

### **Determinants of Hospital Charges for Coronary Artery Bypass Surgery: The Economic Consequences of Postoperative** Complications

George J. Taylor, Frank L. Mikell, H. Weston Moses, James T. Dove, Richard E. Katholi, Shezad A. Malik, Stephen J. Markwell, Cynthia Korsmeyer, Joel A. Schneider, and Harry A. Wellons

Data from 500 consecutive patients undergoing coronary artery bypass were analyzed according to preoperative variables and postoperative complications. No preoperative clinical feature emerged as a significant predictor of higher average charges; development of sternal wound infection, respiratory failure and left ventricular failure were associated with higher than average charges. Complications have a powerful influence on charges for coronary bypass, suggesting that programs with low average charges will have low complication rates.

### 314

### **Attenuation of Exercise-Induced ST Depression During Combined Isometric and Dynamic Exercise in Coronary Artery Disease**

Kim Bertagnoli, Peter Hanson, and Ann Ward

ST depression was compared during dynamic (treadmill) exercise and during combined isometric and dynamic (isodynamic) exercise performed at similar heart rate × systolic pressure product. Eleven male patients (mean age 63 years) with stable coronary artery disease showed 1.5 mm of ST depression during submaximum treadmill exercise (rate-pressure product 18,000). During isodynamic exercise (treadmill walking carrying weights) at an equivalent rate-pressure product (18,600), ST depression

Continued on page A28

### The only beta blocker as effective as quinidine

### ...without quinidine complications.

In randomized, double-blind crossover studies, 1,2 Sectral® (acebutolol HCI) was shown to be as effective as quinidine in reducing spontaneous premature ventricular contractions (PVCs), exercise-induced PVCs and complex PVCs.\* Unlike quinidine, Sectral® was not associated with drug-related gastric discomfort or diarrhea. 1,2 Clinical experience in over 1,000 patients yielded only a 4 percent incidence of diarrhea, constipation or flatulence.

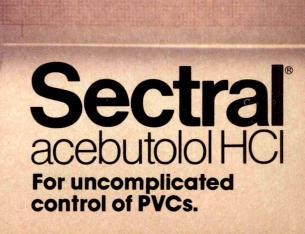
As the investigators commented: "The antiarrhythmic activity of (Sectral®), its ancillary pharmacologic properties, and its tolerance by a diverse group of patients make (Sectral®) a significant tool for the clinician in the management of chronic arrhythmia."<sup>2</sup>

Like other beta blockers, Sectral® is contraindicated in persistently severe bradycardia, second- and third-degree heart block, overt congestive heart failure and cardiogenic shock.

Initiate Sectral® therapy with 200 mg b.i.d. Dosage can be increased gradually until optimal response is obtained, generally between 600 mg to 1200 mg per day.

Please see brief summary on adjacent page.

\*Sectral® is not indicated for ventricular tachycardia.





### For uncomplicated control of PVCs.

(Brief summary of prescribing information)

CONTRAINDICATIONS: SECTRAL is contraindicated in: 1) persistently severe bradycardia; 2)second- and third-degree heart block; 3) overt cardiac failure; and 4) cardiogenic shock. (See

2)second- and third-degree heart block; 3) overt cardiac failure, and 4) calculogeme should WARNINGS) WARNINGS: CARDIAC FAILURE: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by β-adrenergic receptor blockade may precipitate more severe failure. Although β-blockers should be avoided in overt cardiac failure, SECTRAL can be used with caution in patients with a history of heart failure who are controlled with digitalis and/or diuretics. Both digitalis and SECTRAL impair AV conduction. If cardiac failure persists, therapy with SECTRAL should be withdrawn. IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE: In patients with aortic or mitral valve disease or compromised left ventricular function, continued depression of the myocardium with β-blocking agents over a period of time may lead to cardiac failure. At the first signs of failure, patients should be digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues despite adequate digitalization and/or diuretic, SECTRAL therapy should be withdrawn.

failure, patients should be digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues despite adequate digitalization and/or diuretic, SECTRAL therapy should be withdrawn. EXACERBATION OF ISCHEMIC HEART DISEASE FOLLOWING ABRUPT WITHDRAWAL: Following abrupt cessation of therapy with certain  $\beta$ -blocking agents in patients with coronary artery disease, exacerbation of angina pectoris and, in some cases, myocardial infarction and death have been reported. Therefore, such patients should be cautioned against interruption of therapy without a physician's advice. Even in the absence of over itschemic heart disease, when discontinuation of SECTRAL is planned, the patient should be carefully observed, and should be advised to limit physical activity to a minimum while SECTRAL is gradually withdrawn over a period of about two weeks. (If therapy with an alternative  $\beta$ -blocker is desired, the patient may be transferred directly to comparable doses of another agent without interruption of  $\beta$ -blocking therapy). If an exacerbation of angina pectoris occurs, anti-anginal therapy should be restarted immediately in full doses and the patient hospitalized until his condition stabilizes. PERIPHERAL VASCULAR DISEASE: Treatment with  $\beta$ -antagonists reduces cardiac output and can precipitate or aggravate the symptoms of arterial insufficiency in patients with peripheral or mesenteric vascular disease. Caution should be exercised with such patients and they should be observed closely for evidence of progression of arterial obstruction. BRONCHOSPASTIC DISEASE: SHOULD, IN GENERAL, NOT RECEIVE A  $\beta$ -BLOCKER. Because of its relative  $\beta$ -selectivity, however, low doses of SECTRAL may be used with caution in patients with bronchospastic disease who do not respond to, or who cannot tolerate, alternative treatment. Since  $\beta$ -selectivity is not absolute and is dose-dependent, the lowest possible dose of SECTRAL should be used initially, preferably in divided doses to avoid the higher plasma leve

with instructions concerning its use.

ANESTHESIA AND MAJOR SURGERY: The necessity, or desirability, of withdrawal of a β-blocking therapy prior to major surgery is controversial. β-adrenergic receptor blockade impairs the ability of the heart to respond to β-adrenergically mediated reflex stimuli. While this might be of benefit in preventing arrhythmic response, the risk of excessive myocardial depression during general anesthesia may be enhanced and difficulty in restarting and maintaining the heartbeat has been reported with beta-blockers. If treatment is continued, particular care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane and trichiorethylene, and it is prudent to use the lowest possible dose of SECTRAL. SECTRAL, like other β-blockers, is a competitive inhibitor of β-receptor agonists and its effect on the heart can be reversed by cautious administration of such agents (e.g., dobutamine or isoproterenol—see OVERDOSE). Manifestations of excessive vagal tone (e.g., profound bradycardia, hypotension) may be corrected with atropine 1 to 3 mg i v. in divided doses.

DIABETES AND HYPOGLYCEMIA: β-blockers may potentiate insulin-induced hypoglycemia and not significantly affected. Diabetic patients should be warned of the possibility of masked hypoglycemia.

hypoglycemia.

THYHOTOXICOSIS: β-adrenergic blockade may mask certain clinical signs (tachycardia) of hyperthyroidism. Abrupt withdrawal of β-blockade may precipitate a thyroid storm, therefore, patients suspected of developing thyrotoxicosis from whom SECTRAL therapy is to be withdrawn

patients suspected of developing thyrotoxicosis from whom SECTRAL therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: IMPAIRED RENAL OR HEPATIC FUNCTION: Studies on the effect of acebutolol in patients with renal insufficiency have not been performed in the U.S. Foreign published experience shows that acebutolol has been used successfully in chronic renal insufficiency. Acebutolol is excreted through the G.I. tract, but the active metabolite, diacetolol, is eliminated predominantly by the kidney. There is a linear relationship between renal clearance of diacetolol and creatinine clearance. Therefore, the daily dose of acebutolol should be reduced by 50% when the creatinine clearance is less than 50 mL/min and by 75% when it is less than 25 mL/min.

SECTRAL should be used cautiously in patients with impaired hepatic function.

SECTRAL has been used successfully and without problems in elderly patients in the U.S. clinical trials without specific adjustment of dosage. However, elderly patients may require lower maintenance doses because the bioavailability of both SECTRAL and its metabolite are approximately doubled in this age group.

maintenance doses because the bloavailability of both SECTRAL and its metabolite are approximately doubled in this age group. CLINICAL LABORATORY FINDINGS: SECTRAL, like other \$\beta\$-blockers, has been associated with the development of antinuclear antibodies (ANA). In prospective clinical trials, patients receiving SECTRAL had a dose dependent increase in the development of positive ANA titers and the overall incidence was higher than that observed with propranolol. Symptoms (generally persistent arthralgias and myalgias) related to this laboratory abnormality were infrequent (less than 1% with both drugs). Symptoms and ANA titers were reversible upon discontinuation of treatment. INFORMATION FOR PATIENTS: Patients, especially those with evidence of coronary artery disease, should be warned against interruption or discontinuation of SECTRAL therapy without a physician's supervision. Although cardiac failure rarely occurs in properly selected patients, those being treated with \$\beta\$-afernergic blocking agents should be advised to consult a physician if they develop signs or symptoms suggestive of impending CHF, or unexplained respiratory symptoms. Patients should also be warned of possible severe hypertensive reactions from concomitant use of \$\alpha\$-adrenergic blocking agents severe hypertensive reactions from concomitant use of \$\alpha\$-adrenergic stimulants such as the nasal decongestants commonly used in OTC cold preparations and nasal drops.

DRUG INTERACTIONS: Catecholamine-depleting drugs, such as reserpine, may have an

preparations and nasal drops. DRUG INTERACTIONS: Catecholamine-depleting drugs, such as reserpine, may have an additive effect when given with B-blocking agents. Patients treated with SECTRAL plus catecholamine depletors should, therefore, be observed closely for evidence of marked bradycardia or hypotension which may present as vertigo, syncope/pre-syncope, or orthostatic changes in blood pressure without compensatory tachycardia. Exaggerated hypertensive responses have been reported from the combined use of  $\beta$ -adrenergic antagonists and  $\alpha$ -adrenergic stimulants, including those contained in proprietary cold remedies and vaso-constrictive nasal drops. Patients receiving B-blockers should be warned of this potential hazard. No significant interactions with digoxin, hydrochlorothiazide, hydralazine, sulfinpyrazone, oral contraceptives, tolbutamide or warfarin have been observed.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Chronic oral toxicity studies in rats and mice, employing dose levels as high as 300 mg/kg/day, which is equivalent to 15 times the maximum recommended (60 kg) human dose, did not indicate a carcinogenic potential for SECTRAL (acebutolol HCl). Diacetolol, the major metabolite of SECTRAL in man, was without carcinogenic potential in rats when tested at doses as high as 1800 mg/kg/day. SECTRAL and diacetolol were also shown to be devoid of mutagenic potential in the Ames Test. SECTRAL, administered orally to two generations of male and female rats at doses of up to 240 mg/kg/day lequivalent to 12 times the maximum recommended therapeutic dose in (a 60 kg) man) and diacetolol, administered to two generations of male and female rats at doses of up to 1000 mg/kg/day, had no significant impact on reproductive performance or fertility. TERATOGENIC EFFECTS: Pregnancy Category B: Reproduction studies have been performed with SECTRAL in rats and rabbits at doses of up to 450 mg/kg/day, the equivalent of 3 times the maximum recommended therapeutic dose in (a 60 kg) man. Studies have also been performed with SECTRAL in rats and rabbit and to 1800 mg/kg/day in rats). Other than a significant increase in incidence of bilateral cataract in rat fetuses from dams treated with 1800 mg/kg/day diacetolol, there was no evidence of harm to the fetus with either drug. There are no adequate and well-controlled trials in pregnant women in the U.S., however, studies have shown that both acebutolol and diacetolol cross the placent in the fetus with either drug. There are no adequate and well-controlled trials in pregnant women in the U.S., however, studies have shown that both acebutolol and diacetolol cross the placents in the fetus with either drug. There are no adequate and well-controlled trials in pregnant women in the U.S., however, studies have shown that both acebutolol and diacetolol cross the placents in the fetus with either drug. There are no adequate and well-controlled t CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Chronic oral toxicity

unknown. Studies in animals have not shown any effect of SECTRAL on the usual course of labor and delivery.

Nursing Mothers: Acebutolol and diacetolol also appear in breast milk with a milk:plasma ratio of 7.1 and 12.2, respectively. Use in nursing mothers is not recommended.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: SECTRAL is well tolerated in properly selected patients. Most adverse reactions have been mild, not required discontinuation of therapy, and tended to decrease as duration of treatment increases.

The following table shows the frequency of treatment-related side effects derived from

The following table shows the frequency of treatment-related side effects derived from controlled clinical trials in patients with hypertension, angina pectoris, and arrhythmia. These patients received SECTRAL, propranolol, or hydrochlorothiazide as monotherapy, or placebo

### TOTAL VOLUNTEERED AND ELICITED (U.S. STUDIES)

Body System/ Adverse Reaction	SECTRAL (N=1002)	Propranolol (N=424) %	thiazide (N=178)	Placebo (N=314)
Cardiovascular			Mark The Control	
Chest Pain	2	4	4	1
Edema	2	2	4	1
Central Nervous Sy	stem			
Depression	2	1	3	1
Dizziness	6	7	12	2 4
Fatigue	11	17	10	4
Headache	6	9	13	4
Insomnia	3	6	5	
Abnormal				
dreams	2	3	0	
Dermatologic				THE RESERVE
Rash	2	2	4	
Gastrointestinal				0
Constipation	4	2		0
Diarrhea	4	2 5 6	7 5 3 7 3	
Dyspepsia	4	6	3	
Flatulence	3	4		
Nausea	4	Ь	3	0
Genitourinary	3		9	
Micturition	3		9	<1
(frequency)				
Musculoskeletal	0	TO STORY WAS A STREET		0
Arthralgia	2 2		3 4	2 0
Myalgia	2		4	0
Respiratory	Harrison Fred		0	0
Cough	4	6	2 4	0 2 <1
Dyspnea Rhinitis	2	0	4	11
	2		4	
Special Senses Abnormal Vision	2	2	3	0
AUTOTINAL VISION	6	2	0	0

The following selected (potentially important) side effects were seen in up to 2% of SECTRAL patients. Cardiovascular. hypotension, bradycardia, heart failure. Central Nervous System: anxiety, hyper/hypoesthesia, impotence. Deermatological: pruritus. Gastrointestinal: vomiting, abdominal pain. Genitourinary: dysuria, nocturia. Musculoskeletal: back pain, joint pain. Respiratory: pharyngitis, wheezing. Special Senses: conjunctivitis, dry eye, eye pain. The incidence of drug-related adverse effects (volunteered and solicited) according to SECTRAL dose is shown below. (Data from 266 hypertensive patients treated for 3 months on constant dose).

	400 mg/ day	800 mg/ day	1200 mg/ day	
Body System	(N=132)	(N=63)	(N=71)	
Cardiovascular	5%	2%	1%	2.119
Gastrointestinal	3%	3%	7%	
Musculoskeletal	2%	3%	4%	
Central Nervous				
System	9%	13%	17%	
Respiratory	1%	5%	6%	
Skin	1%	2%	1%	
Special Senses	2%	2%	6%	
Senitourinary	2%	3%	1%	

POTENTIAL ADVERSE EFFECTS: In addition, certain adverse effects not listed above have been reported with other β-blocking agents and should also be considered as potential adverse effects of SECTRAL

effects of SECTRAL.

Central Nervous System: Reversible mental depression progressing to catatonia (an acute syndrome characterized by disorientation for time and place), short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance (neuropsychometrics).

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS).

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm, and respiratory distress.

Hematologic: Agranulocytosis, non-thrombocytopenic, and thrombocytopenic purpura.

Gastrointestinal: Mesenteric arterial thrombosis and ischemic colitis.

Miscellaneous: Reversible alopecia and Peyronie's disease. The coulomucocutaneous syndrome associated with the β-blocker practoloi has not been reported with SECTRAL during investigational use and extensive foreign clinical experience.

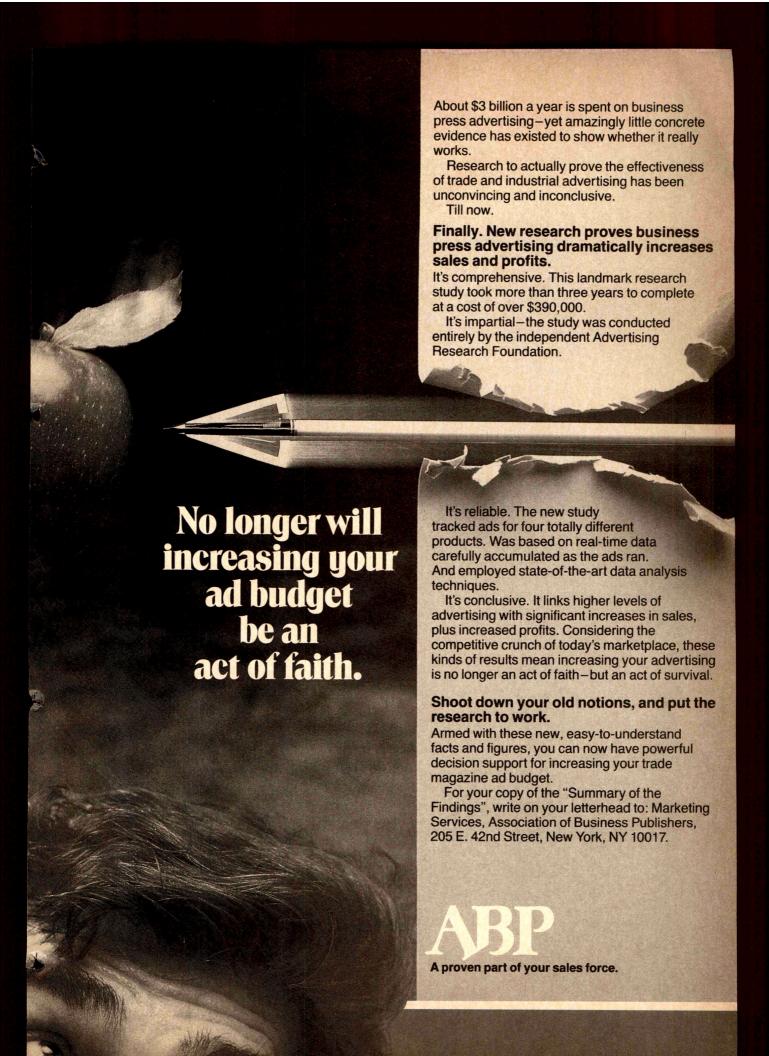
### Keep at room temperature. Approximately 25°C (77°F).

\*Sectral® is not indicated in ventricular tachycardia

- Shapiro W, Park J, Koch GG: Variability of spontaneous and exercise-induced ventricular arrhythmias in the absence and presence of treatment with acebutolol or quinidine. Am J Cardiol 1982;49:445-454.
   Chandraratna PAN: Compairson of acebutolol with propranolol, quinidine, and placebo: Results of three multicenter arrhythmia trials. Am Heart J 1985;109:1198-1204.



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was only 0.4 mm. These results were reproducible on repeated tests and were not influenced by the order of testing. We conclude that rate-pressure product is not a valid index of ST response during isodynamic exercise. Attenuation of ST depression during isodynamic exercise may be due to significantly higher diastolic perfusion pressure (+25 mm Hg) and reduction of venous return due to increased intrathoracic and abdominal pressure.

### ARRHYTHMIAS AND CONDUCTION DISTURBANCES

### Relation of Syncope in Young Patients with Wolff-Parkinson-White Syndrome to Rapid Ventricular Response During **Atrial Fibrillation**

Thomas Paul, Paolo Guccione, and Arthur Garson, Jr.

Occurrence of atrial fibrillation (AF) with a rapid ventricular response over the accessory pathway during electrophysiologic study in 74 young patients ≤25 years old (mean age 12.6 years) with Wolff-Parkinson-White (WPW) syndrome provided high sensitivity and specificity to identify patients with a history of syncope (n = 14). Sustained (>5 minutes or requiring termination due to hypotension) AF occurred only in 9 of 14 patients with syncope; none of the 60 patients without syncope had sustained AF. All patients with syncope and AF (n = 12) had a short RR interval between 2 consecutive preexcited QRS complexes during AF of ≤220 ms in contrast to 9 of 34 patients without syncope. No patient with a short RR interval between 2 consecutive preexcited QRS complexes during AF of >220 ms had a history of syncope. Thus, electrophysiologic study may be helpful in identification of young WPW patients at risk of syncope.

### Value of Esophageal Pacing in Evaluation of Supraventricular **Tachycardia**

Béatrice Brembilla-Perrot, Frédéric Spatz, Ewad Khaldi, Arnaud Terrier de la Chaise, Diem Le Van, and Claude Pernot

To look for a sensitive stimulation protocol and for criteria to define the mechanism of reentry, we performed esophageal stimulation in 40 patients who had spontaneous paroxysmal supraventricular tachycardias. Supraventricular tachycardias could be uniformly induced by programmed atrial stimulation in the control state and under isoproterenol; the location of the P wave in V<sub>1</sub> compared to the ventriculogram and the esophageal electrocardiogram helped to define the mechanism of tachycardia.

Continued on page A35



## < 35<sub>HDL</sub>

### What's a common denominator of most heart attack victims?

Mixed hyperlipidemias—elevated cholesterol and triglycerides—are common among heart attack victims,<sup>1</sup> and nearly two thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.<sup>2</sup>

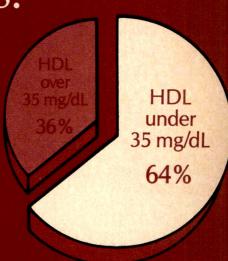
HEART ATTACK PATIENTS (PROCAM TRIAL)<sup>2</sup>

### LOPID raised low HDL 25%

—in patients whose baseline HDL was below 35 mg/dL in the landmark Helsinki Heart Study (HHS).<sup>3</sup>

### Reduced heart attack incidence\* up to 62%

—in these HHS patients and 45% in HHS patients whose baseline HDL was below the median (46.4 mg/dL). Incidence of serious coronary events was similar for LOPID and placebo subgroups with baseline HDL above the median (46.4 mg/dL).<sup>3</sup>



## A powerful case for [OPID] BID BID (gemfibrozil) 600-mg Tablets

### RAISES HDL...DRAMATICALLY REDUCES HEART ATTACK

LOPID is indicated for reducing the risk of coronary heart disease (CHD) in Type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequestrants and nicotinic acid.

\*Defined as a combination of definite coronary death and/or definite myocardial infarction

References: 1. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. J Clin Invest. 1973;52:1533-1543. 2. Assmann G, Schulte H. PROCAM-Trial: Prospective Cardiovascular Münster Trial. Zürich: Panscientia Verlag; 1986:8-9. 3. Data on file, Medical Affairs Dept, Parke-Davis.

Please see adjacent page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

**PARKE-DAVIS** 

© 1989 Warner-Lambert Company

Lopid® (Gemfibrozil Capsules and Tablets)

Before prescribing, please see full prescribing information. A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary

Preexisting gallbladder disease (See WARNINGS)

sensitivity to gemfibrozil.

**WARNINGS.** 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, postcholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treate subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056)

In the Helsinki Heart Study, the incidence of total malignancies discovered during the in the Heisinki Heart Study, the incidence of total manignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths

from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further infor mation on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the place bo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% ex-cess). This result did not differ statistically

from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants — Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications.

Frequent prothrombin determinations are advisable until it has been definitely determined. that the prothrombin level has stabilized.

 Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3%

of nale rats reated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. Initial Therapy—Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight los in obese patients, and control of any medical problems such as diabetes mellitus and

pothyroidism that are contributing to the lipid abnormalities.

2. Continued Therapy — Periodic determination of serum lipids should be obtained,

and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. Drug Interactions—(A) Lovastatin: Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhab-domyolysis, and acute renal failure. There is no assurance that periodic monitoring of

creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTI-COAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. Carcinogenesis, Mutagenesis, Impairment of Fertility — Long-term studies have been conducted in rats and mice at one and ten times the human dose. The inci dence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences Lopid® (Gemfibrozil Capsules and Tablets)

from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome prolifera-tion following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were com-

pared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring

5. Pregnancy Category B - Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those pa-

tients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. Nursing Mothers – Because of the potential for tumorigenicity shown for gem fibrozil in rats, a decision should be made whether to discontinue nursing or discontinue

the drug, taking into account the importance of the drug to the mother.

7. Hematologic Changes – Mild hemoglobin, hematocrit and white blood cel decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. Liver Function – Abnormal liver function tests have been observed occasionally

during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bili-rubin, and alkaline phosphatase. These are usually reversible when Lopid is discon-tinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children**—Safety and efficacy in

not been established ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in paren-

theses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but

adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular

disease, and intracerebral hemorrhage.
From other studies it seems probable that Lopid is causally related to the o of musculoskeletal symptoms (See WARNINGS), and to abnormal liver function tests and hematologic changes (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients

Additional adverse reactions that have been reported for gemfibrozil are listed below

by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:
CAUSAL RELATIONSHIP PROBABLE: Gastrointestinal: cholestatic jaundice; Central

Nervous System: dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; Eye: blurred vision; Genitourinary: impotence; libido, depression, fleadache; Eye: blurred vision; Geriticumary. Impotence; Musculoskeletal: myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); Clinical Laboratory: increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; Hematopoietic: anemia, leukopenia, bone marrow hypoplasia, eosinophilia; Immunologic: angioedema, laryngeal edema, urticaria; Integumentary: exfoliative der

CAUSAL RELATIONSHIP NOT ESTABLISHED: General: weight loss; Cardiac: extrasystoles; Gastrointestinal: pancreatitis, hepatoma, colitis; Central Nervous System: confusion, convulsions, syncope; Eye: retinal edema; Genitourinary: decreased male fertility; Clinical Laboratory: positive antinuclear antibody; Hematopoietic: thrombocytopenia; Immunologic: anaphylaxis. Lupus-like syndrome, vasculitis; Integumentary: alopecia. Immunologic: anaphylaxis, Lupus-like syndrome, vasculitis; Integumentary: alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. N Engl J Med

1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the Medical Medical Research Proceedings of the Medical MH, 1989. in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of

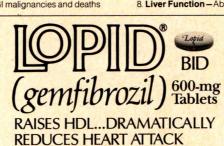
chylomicron metabolism. In Stanbury J. B. et al. (eds.): *The Metabolic Basis of Inherited Disease*, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642. **Caution** — Federal law prohibits dispensing without prescription.

PARKE-DAVIS Morris Plains, NJ 07950 USA

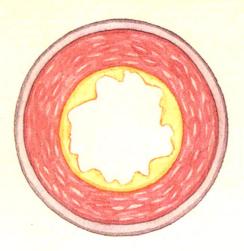
matitis, rash, dermatitis, pruritus

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PD-56-JA-5932-A-1(12-89)



### **Hardhearted**

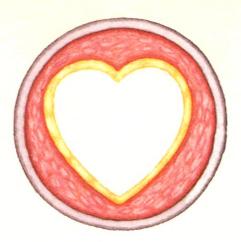


### **Thiazide Diuretics**

In study after study, they have been associated with increases in cholesterol.

And now, the Lipid Research Clinics Trial has established a clear link between elevated lipids and risk of coronary heart disease. Thiazide diuretics are also known to cause potassium depletion, which, untreated, can lead to cardiac arrhythmias.

### **Kindhearted**



### LOZOL® (indapamide) alone

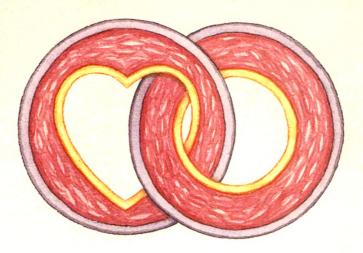
In long-term clinical trials, Lozol has demonstrated little or no effect on serum cholesterol levels.<sup>2-4\*</sup>

Lozol also has minimal impact on potassium, with 95% of patients showing no clinical hypokalemia in a long-term trial.<sup>2†</sup>

<sup>\*</sup>Lozol is not a cholesterol-lowering agent, nor has it been shown to reduce existing atherosclerotic plaque.

<sup>†</sup>Because of the diuretic effects of Lozol, changes in certain electrolytes can occur. Determination of serum electrolytes should therefore be performed.

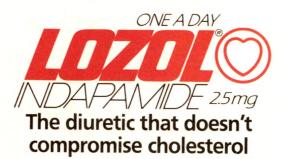
### Compatible



### LOZOL + ACE inhibitor or calcium antagonist

Like ACE inhibitors and calcium antagonists, Lozol lowers blood pressure without compromising cholesterol or potassium.

That makes Lozol the diuretic to choose for kindhearted add-on antihypertensive therapy.



Please see brief summary of prescribing information on the following page.

### **Kindhearted and Compatible**





The diuretic that doesn't compromise cholesterol

### LOZOL® indapamide 2.5 mg tablets

Brief Summary

DESCRIPTION: Lozol® indapamide) is an oral antihypertensive/diuretic.

INDICATIONS AND USAGE: Lozol is indicated for the treatment of hypertension, alone or in combination with other antihypertensive dup.

Lozol is also indicated for the treatment of salt and fluid retention associated with conpestive heart failure.

congestive heart failure.

Usage in Pregnancy: (see PRECAUTIONS).

CONTRAINDICATIONS: Anuria. Known hypersensitivity to indapamide or to other sulfonamide-derived drugs.

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In general, our sound as the processible of the proce

function tests should be performed periodicity during treatment with mappamole 4. Mapitand Pepal Function Indiagamide, like the thistolies, should be used with cau-ching the periodic periodic properties of the periodic periodi

of glucose should be monitored routinely during treatment with Lozol.

6 *Caclium Excellar Caclium acresteron is decreased by durints cybarnacologically* related to indapamide. In long-term studies of hyportensive patients, however, serum concentrations of caclium increased only slightly with indapamide. Prolonged treatment with drugs pharmacologically related to indapamide may in are instances be associated with pytericalizems and hypophospharmas secondary to hypisologic changes in the parathyrou gland, however, the common complications of hyperparathyroidism, such as parathyroid gland, however, the common complications of hyperparathyroidism, such as parathyroid gland, however, the common complications of hyperparathyroidism, such as indiapamide may discrease serum PBI levels without signs of thyroid disturbance. *Thireaction With Systemic Lugus Cythymentasius*: Thiratels have exacteristated or activated systemic lugus erythematosus: Tairces have exacteristated or activated systemic lugus erythematosus: Tairces have exacteristated or activated systemic lugus erythematosus and this possibility should be considered with midapamide as Weight and the considered with midapami

indapamide as well.

DBUG INTERACTIONS: 1. Other Anthypertensives: Lozol (indapamide) may add to or potentiate the action of other anthypertensive drugs. In limited controlled traits that compared the effect of indapamide combined with other anthypertensive drugs with the effect of the other drugs administered alone, there was no notable charge in the nature or requirecy of adverse teactions associated with the combined therapy.

2. Influent Dee WARHWIGS.

Limitude 300 WANNINGS.

Post-Sympathectomy Patient: The antihypertensive effect of the drug may be hanced in the post-sympathectomized patient.

3. Post sympathectomy relatent. The antihypertensive effect of the drug may be enhanced in the post-sympathectomized patient.

4. Novepimphrine: Indupaming, like the thizaides, may decrease atterial responsiveness processing the control of the process of the process of the process regard for the report of the process regard for the report of the process of the process regard for the report of the process of the process regard for the report of the process of the proc

LOZO.

When SupPLIED: Lozol (indapamide). White, round film-coated tablets of 2.5 mg in bottles of 100 (NDC 0075-0082-00), 1,000 (NDC 0075-0082-9), and in unit-dose bilister packs, boses of 100 (10 x 10 x trips) (NDC 0075-0082-9), and in unit-dose bilister packs, boses of 100 (10 x 10 x trips) (NDC 0075-0082-8).

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescribed. Ree putply closed. Store at room temperature, avoid excessive heat. Dispense in tight containers as defined in USP.

See product crucial for full prescribing information. Revised: November 1988 (AS)

Reference: 1. Lipid Research Clinics Program: The Lipid Research Clinics Coronary Primary Prevention Trai results. I Reduction in incidence of coronary Neural disease.

JAMA 1984; 251: 351-354. 2, Belling S, Vukovich RA, Neiss ES, et al. Long-term experience with indigame. Am Heart J 1983: 100: 528-626. 3. Meyer-Sabellet W, Gotzer R, Heltz J, et al. Serum lipoprotein levels during long-term treatment of hypertension vigos/Crupp 2, 1770-174. 4 Wendmann P. Geber A Effects of treatment with districts on serum lipoproteins. J Cardiovasc Pharmacol 1984; 6. Suppl 1, 1200-126.



### RORER PHARMACEUTICALS

ROBER PHARMACEUTICAL CORPORATION Fort Washington, PA, U.S.A. 19034

Product of Servier Research Institute See product circular for full prescribing information. © 1989 Rorer Pharmaceutical Corporation LZ06190A 1/90 FC#90-114

#### **SYSTEMIC HYPERTENSION**

331

Comparison of Long-Term Hemodynamic Effects at Rest and During Exercise of Lisinopril Plus Sodium Restriction Versus Hydrochlorothiazide in Patients with Essential Hypertension Per Omvik and Per Lund-Johansen

The long-term hemodynamic effects of lisinopril in combination with moderate sodium restriction or hydrochlorothiazide were compared in patients with essential hypertension to investigate whether sodium restriction might replace thiazides to potentiate the antihypertensive effect of angiotensin-converting enzyme inhibition. Both treatment combinations induced marked reduction in blood pressure due to decreases in peripheral vascular resistance both at rest and during exercise. Due to a reduction in cardiac output the reduction in blood pressure was greater with lisinopril plus hydrochlorothiazide than with lisinopril plus low salt diet. However, since lisinopril plus low salt diet leads to a more complete normalization of central hemodynamics with less metabolic side effects, this combination should be preferred when satisfactory blood pressure control is obtained.

339

# Effect of Postural Stimulation on Systemic Hemodynamics and Sympathetic Nervous Activity in Systemic Hypertension

Joseph L. Izzo, Jr., Emilee Sander, and Patricia S. Larrabee

We studied 68 mildly hypertensive subjects and measured supine and upright plasma norepinephrine, blood pressure (cuff) and cardiac output (acetylene rebreathing). Mean arterial pressure (MAP), carotid sinus MAP, stroke volume and systemic vascular resistance were calculated. We assumed that stroke volume is proportional to the degree of stretch of cardiac mechanoreceptors, that carotid sinus MAP is proportional to carotid sinus stretch and that plasma norepinephrine reflects sympathetic activity. Plasma norepinephrine correlated inversely with stroke volume (r = -0.62, p  $< 10^{-14}$ ) and carotid sinus MAP (r = -0.33, p < 0.0002) and positively with systemic vascular resistance (r = 0.59, p <  $10^{-10}$ ). Holding systemic resistance constant by partial regression, the inverse relation between plasma norepinephrine and stroke volume remained (partial r = -0.36, p <0.0002). Multiple linear regression yielded the equation plasma norepinephrine (pg/ml) = 720 + 4.3 age - 5.1 stroke volume (ml) -1.0 carotid sinus MAP (mm Hg). To the extent that changes in stroke volume reflect altered cardiac stretch, it can be inferred that cardiopulmonary baroreflexes are primary activators of the sympathetic system in postural adaptation.

#### **CONGESTIVE HEART FAILURE**

343

**Usefulness of Nicorandil in Congestive Heart Failure** 

Nazzareno Galiè, Elisabetta Varani, Luigi Maiello, Giuseppe Boriani, Stefano Boschi, Giorgio Binetti, and Bruno Magnani

Rest and exercise hemodynamic and hormonal effects of nicorandil, a nicotinamide-nitrate vasodilator, were assessed in 9 patients with congestive heart failure. Single oral doses of placebo and 40 and 60 mg of nicorandil were given in a double-blind, randomized trial. Peak effects were observed between 30 and 60 minutes and the hemodynamic changes were significant up to 6 to 8 hours. Nicorandil decreased mean blood pressure, mean pulmonary artery and wedge pressures and increased venous capacitance and cardiac output at rest. It also decreased mean pulmonary wedge pressure at peak exercise and increased cardiac output 1 hour after the meal. Plasma renin activity was increased by nicorandil.

#### **VALVULAR HEART DISEASE**

Follow-Up in Mitral Valve Prolapse by Phonocardiography, M-Mode and Two-Dimensional Echocardiography and Doppler **Echocardiography** 

Deng You-Bing, Katsu Takenaka, Tsuguya Sakamoto, Yoshiyuki Hada, Jun-ichi Suzuki, Takahiro Shiota, Wataru Amano, Tsutomu Igarashi, Keiko Amano, Hisako Takahashi, and Tsuneaki Sugimoto

Follow-up phonocardiograms and echocardiograms were studied in 116 patients with mitral valve prolapse at an interval of 4.3 years (range 1 to 14 years). Although the degree of prolapse assessed by 2-dimensional echocardiography was unchanged, both phonocardiography and Doppler echocardiography showed an increase in the incidence of mitral regurgitation. M-mode echocardiography revealed increases in left atrial and ventricular sizes in patients with systolic murmur.

In Vivo Identification of Mitral Valve Fibrosis and Calcium by **Real-Time Quantitative Ultrasonic Analysis** 

Fabio Lattanzi, Eugenio Picano, Luigi Landini, Alessandro Mazzarisi, Gualtiero Pelosi, Antonio Benassi, Leonardo Salvatore, Alessandro Distante, and Antonio L'Abbate

Thirty-three patients, scheduled to undergo mitral valve replacement, and 10 young control subjects were studied with a 2.25-MHz transducer. Radiofrequency signal was analyzed by a microprocessor system (integrated with a commercially available M-mode system) for on-line evalua-

Continued on page A41

# NEW EMANASE® ANISTREPLASE 300

APSAC

Manufactured by:
Beecham-Wülfing
Neuss, West Germany
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9 1990 SmithKline Beecham Pharmaceuticals

See insert in this issue for additional product information.

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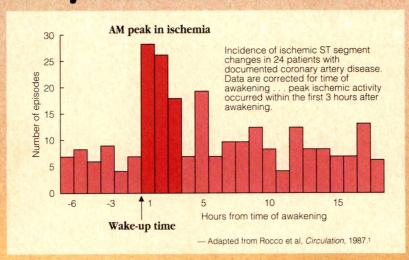
SB SmithKline Beecham



Upjohn

# As predictable as the sunrise...

# The morning rise in myocardial ischemia<sup>1</sup>



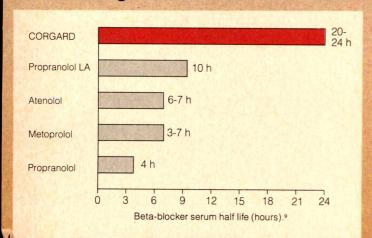
Studies indicate that a similar circadian pattern also exists for:

- -Myocardial infarction<sup>2</sup>
- -Sudden cardiac death<sup>3</sup>
- -Ischemic stroke4
- -Heart rate<sup>5</sup>
- -Blood pressure<sup>5</sup>
- -Plasma catecholamines<sup>6</sup>
- -Platelet aggregation.6

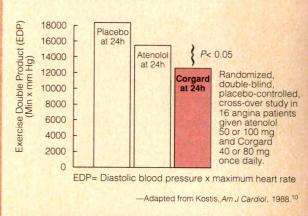
# CORGARD

# 24-hour antianginal protection... throughout the circadian pattern of myocardial ischemia<sup>7</sup>

Corgard: The beta blocker with the longest duration of action8... and the longest half life9



Corgard: Significantly greater suppression of exercise double product than atenolol at 24 hours<sup>10</sup>



CORGARD<sup>®</sup>
(nadolol tablets)
On guard, 24 hours a day

Please see brief summary of prescribing information on adjacent page.

# CORGARD® (nadolol tablets)

# On guard, 24 hours a day











CORGARD\* TABLETS Nadolol Tablets USP

DESCRIPTION: CORGARD (nadolol) is a synthetic nonselective beta-adrenergic receptor block

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure-Sympathetic stimulation may be a vital component supporting ulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitat more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diurelics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal-Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. When discontinuing chronic use of nadolol, particu-larly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of beta, receptors.

Major Surgery-Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to calectolamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

**Diabetes and Hypoglycemia**—Beta-adrenergic blockade may prevent the appearance of pre-monitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypogly-cemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND AD-MINISTRATION section of package insert).

Information for Patients-Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolo without physician's advice. Although pardiac failure rarely occurs in property selected patients, advise patients being treated with bate. cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Prug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hypogrylycemia, adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect; monitor closely for hypotension and/or excessive bradycardia

Carcinogenesis, Mutagenesis, Impairment of Fertility-In 1 to 2 year oral toxicologic stud mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcino-c studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions

Pregnancy Category C—In animal reproduction studies with nadolol, evidence of embryo- and totoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in

pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who red nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptom

Nursing Mothers-Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely

Cardiovascular - Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/ conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS, Central Nervous System—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthetral Nervous System—Dizziness or fatigue reported in approximately 2 of 1000 patients; parestinesias, sedation, and change in behavior reported in approximately 6 of 1000 patients.

Respiratory—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). Gastrointestinal—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. Miscellaneous—Each of the following reported in 1 to 5 of 1000 patients: rash; prurifus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible

to the following adverse reactions have been reported in patients taking nadolol and/or other eta-adrenergic blocking agents, but no causal relationship to nadolol has been established. Central Nervous System-reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time turbances; nallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrom-bocytopenic purpura. **Allergic**—fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**— pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

**OVERDOSAGE:** Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a beta<sub>2</sub>-stimulating agent and/or a theophylline derivative.

DOSAGE-For all patients, DOSAGE MUST BE INDIVIDUALIZED

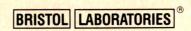
For **angina pectoris**, usual initial dose is 40 mg qd; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg qd (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension**, usual initial dose is 40 mg qd; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg qd (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage

For full prescribing information consult package insert.

HOW SUPPLIED: In scored tablets containing 20, 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100. The 40 mg, 80 mg, and 120 mg tablets are available in bottles of 1000 tablets. The 20 mg, 40 mg, and 80 mg tablets are also available in Unimatic\* unit-dose packs of 100 table



References: 1. Rocco MB, Barry J, Campbell S, et al: Circadian variation of transient myocardial ischemia in patients with coronary artery disease. Circulation 75:395-400;1987. 2. Muller JE, Stone PH, Turi ZG, et al: Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med 313:1315-1322;1985. 3. Willich SN, Levy D, Rocco MB, Tofler GH, Stone PH, Muller JE: Circadian variation in the incidence of sudden cardiac death in the Framingham Heart Study population. Am J Cardiol 60:801-806;1987. 4. Marler JR, Price TR, Clark GL, et al: Morning increase in onset of ischemic stroke. Stroke 20:473-476;1989. 5. Millar-Craig MW, Bishop CN, Raftery EB: Circadian variation of blood-pressure. Lancet 1:795-797;1978. 6. Tofler GH, Brezinski D, Schafer AI, et al: Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden cardiac death. N Engl J Med 316:1514-1518;1987. 7. Kostis JB, Lacy CR, Krieger SD, et al: Atenolol, nadolol, and pindolol in angina pectoris on effort: effect of pharmacokinetics. Am Heart J 108:1131-1136;1984. 8. Vukovich RA, Foley JE, Brown B, et al: Effect of B-blockers on exercise double product (systolic blood pressure × heart rate). Br J Clin Pharmacol 7(suppl 2): 167S-172S;1979. 9. Physicians' Desk Reference®, ed 43, Medical Economics Company, Inc., Oradell, NJ, 1989, pp. 969, 1037, 1635, 2306, 2308. 10. Kostis JB: Comparison of the duration of action of atenolol and nadolol for treatment of angina pectoris. Am J Cardiol 62:1171-1175;1988.

tion of ultrasonic backscatter. The integrated value of the rectified radiofrequency signal amplitude was taken as integrated backscatter index. The highest value recorded with the ultrasonic analysis from each valve was taken as representative and expressed as a percent value with respect to the pericardial integrated backscatter index value of that subject. The 33 excised mitral valves underwent histologic examination. Three groups of subjects were identified: controls (group I, n = 10), patients with fibrotic mitral valve (group II, n = 13) and patients with calcific mitral valve (group III, n = 20). A statistically significant (p < 0.01) difference was noted among the 3 groups for the percent integrated backscatter index value: group I:  $5 \pm 2$  (mean  $\pm$  standard deviation); group II:  $17 \pm 9$ ; and group III: 52 ± 30. In conclusion, a microprocessor-based system for online evaluation of radiofrequency ultrasonic signal is able to differentiate normal, fibrotic and calcific mitral valves in vivo.

#### CARDIOMYOPATHY

## 360

## Angiographic and Electrophysiologic Substrates of Ventricular Tachycardia in Chronic Chagasic Myocarditis

Angelo A.V. de Paola, Leonard N. Horowitz, Mauro H. Miyamoto, Ronaldo Pinheiro, Dario F. Ferreira, Armenio B. Terzian, Claudio Cirenza, Nei Guiguer, Jr., Oscar P. Portugal, and Eulogio E. Martinez Fo

Forty-three consecutive patients with symptomatic ventricular tachycardia (VT) complicating Chagasic myocarditis underwent evaluation with 24-hour Holter monitoring, cardiac catheterization and electrophysiologic study. Electrocardiographic conduction disturbances and left ventricular aneurysm were more common in patients with sustained VT. In patients with clinical nonsustained VT, inducible sustained monomorphic VT was more common in patients with heart failure and a lower ejection fraction. An association appears to be present between conduction disturbances on the electrocardiogram, left ventricular dysfunction and development of sustained VT.

#### 364

## Regional Left Ventricular Wall Motion Abnormalities in Dilated **Idiopathic Cardiomyopathy**

Katharina Stibrant Sunnerhagen, Valmik Bhargava, and Ralph Shabetai

We evaluated and compared left ventricular regional wall motion in 32 patients with idiopathic dilated cardiomyopathy and 17 control subjects, using a frame by frame video intensity-based analysis of digitized ventriculograms. This technique evaluates the whole cardiac cycle in short overlapping intervals and yields information for systolic and diastolic events, without assumptions regarding the position, location and orientation of the ventricle. Regional wall motion abnormalities were found in diastole in 31 of 32 patients and in systole in 16 patients. Asynchronous regions most commonly detected during relaxation were anteroapical and apical (19 of 31 patients). Regional contraction abnormality was observed in the apical and the anteroapical regions in 6 of 16 patients (with systolic abnormality).

### **MISCELLANEOUS**

## 371

## Association of Echocardiographic Left Ventricular Mass with **Body Size, Blood Pressure and Physical Activity** (The Framingham Study)

Daniel D. Savage, Daniel Levy, Andrew L. Dannenberg, Robert J. Garrison, and William P. Castelli

Left ventricular (LV) hypertrophy has been found to predispose to increased cardiovascular morbidity and mortality. To assess the clinical correlates and potential determinants of LV mass, we examined the relationship of echocardiographically determined LV mass to a variety of clinical parameters in 4,972 subjects of the Framingham Heart Study (mean age 51 years) who underwent routine evaluation. Age, height, systolic blood pressure and body mass index (a measure of obesity) were statistically significant and independent correlates of LV mass in both sexes (p <0.001). In men under age 50, leisure-time physical activity was associated with LV mass (p < 0.05), but this was not observed in women. Results from multivariate analyses suggest that lean body mass is correlated with LV mass. Maintenance of ideal body weight and normal blood pressure, weight reduction in obese persons and blood pressure control in hypertensive patients may contribute to the primary and secondary prevention of LV hypertrophy and its sequelae.

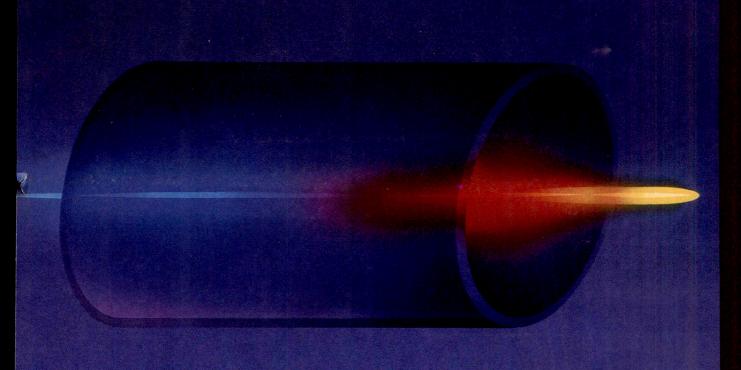
#### 377

## Effect of Alteration in Loading Conditions on Both Normal and Abnormal Patterns of Left Ventricular Filling in Healthy **Individuals**

Thomas R. Downes, Abdel-Mohsen Nomeir, Kathy Stewart, Michael Mumma, Richard Kerensky, and William C. Little

Doppler analysis of mitral flow provides a means of analyzing left ventricular (LV) filling. While conditions that impair LV relaxation reduce early diastolic flow, changes in left atrial pressure may also affect the pattern of filling. The effect of such changes on abnormal patterns of filling is unknown. Accordingly, the Doppler pattern of LV filling was analyzed in 20 subjects with LV hypertrophy, in 25 normal and in 11 healthy elderly subjects at rest and immediately after postural changes. In all 3 groups, head-down positioning raised the E/A ratio. However, in no case did an

Continued on page A48

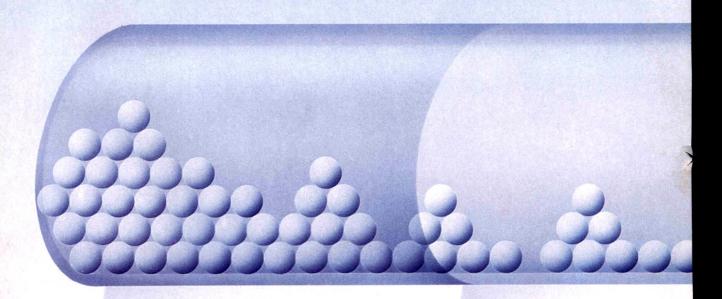


Evidence directly linking elevated cholesterol and CAD made you take a closer look at lipid levels

BUTTHERE'S MORE...

Lorelco is indicated for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia, as an adjunct to diet.

# LOWERING ELEVATED MAY BE JUST



# Lorelco (probucol) offers proven longterm cholesterollowering efficacy \*

- Reduces total cholesterol by up to 27%<sup>1,2</sup>
- Maintains lower levels, as proven over a 12-year period<sup>3</sup>
- Provides the assurance of extensive clinical experience

\*The effect of probucol-induced reduction of serum cholesterol or triglyceride levels or reduction of HDL-cholesterol levels on morbidity or mortality due to coronary heart disease has not been established.

References: 1. S Afr Med J 1982;62:7-11. 2. Arch Intern Med 1981;141:1428-1432.
3. Data on file, MERRELL DOW PHARMACEUTICALS INC., Cincinnati, Ohio 45242-9553. 4. Am J Cardiol 1988;62:318-368. 5. Atherosclerosis 1986;62:209-217.
6. Proc Natl Acad Sci USA 1987;84:5928-5931. 7. J Clin Invest 1986;77:641-644.
8. Proc Natl Acad Sci USA 1987;84:7725-7729. 9. Am J Cardiol 1988;62:68-128.
10. Am J Cardiol 1986;57:16H-21H. 11. Am J Cardiol 1988;62:578-598. 12. Am J Cardiol 1988;62:578-598. 12. Am J Cardiol 1988;62:528-568.

# Lorelco affects cholesterol in unique ways<sup>†</sup>

- Inhibits the oxidative modification of LDL<sup>4-10</sup>
- Enhances HDL-mediated reverse cholesterol transport\*§3

†Unique modes of action suggested by recenin vitro studies and human and/or animal in vivo data; clinical significance, however, is not yet established.

‡These effects of probucol on LDL-(increase in abolic rate) and HDL-cholesterol may be linked observed increased excretion of fecal bile acids, final metabolic pathway for elimination of choles from the body. (See Clinical Pharmacology.)

§The probable benefits obtained from LDL-choles reduction must be weighed against the possible ris of a reduction in HDL-cholesterol when assessing the response of each patient receiving treatment with Lorelco. If satisfactory lipid alteration is not achieved the drug should be discontinued. (See Precautions.)

# LEVELS THE BEGINNING

# LORELCO PROBUCOL

# Lorelco provides important patient compliance benefits

- Convenient dosage—just one 500 mg tablet b.i.d. with meals
- Well tolerated—the most frequent side effect is loose stools, which occurs in about one in ten patients and generally subsides during continued therapy.
   See Prescribing Information for full discussion of side effects.
- Economical—can offer significant cost savings vs most other cholesterol-lowering therapies

Lorelco is not an innocuous drug and strict attention should be paid to the Indications, Contraindications, Warnings, and Precautions sections of Prescribing Information.



TAKES YOU TO THE NEXT LEVEL OF CHOLESTEROL CONTROL

See Prescribing Information appearing on next page.

Merrell Dow U.S.A.

# Lorelco® Tablets (probucol)

CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION: Lorelco (probucol) film-coated tablets for oral administration contain 250 mg or 500 mg of probucol per tablet. Each tablet also contains as inactive ingredients: corn starch, ethylcellulose, glycerin, hydroxypropyl cellulose, hydroxypropyl methylcellulose 2910, iron oxide, lactose, magnesium stearate, microcrystalline cellulose, polysorbate 80, talc, and titanium dioxide, Lorelco is an agent for the reduction of elevated serum closterol. The chemical mane is 4.4" [(1-methyl-ethyli)phenol]. Its chemical structure does not resemble that of any other available cholesterol-lowering agent. It is lipophilic.

CLINICAL PHARMACOLOGY: Lorelco lowers total serum cholesterol and has relatively little effect on serum triglycendes. Patients responding to probucol exhibit a decrease in low-density lipoprotein (LDL) cholesterol. Cholesterol is reduced not only in the LDL traction, but also in the high-density lipoprotein (LDL) traction with proportionately greater effect on high-density portion. Epidemiologic studies have shown that both low HDL-cholesterol and high LDL-cholesterol are independent risk factors for cornery heart disease. The risk of lowering HDL-cholesterol while lowering LDL-cholesterol remains unknown. There is little or no effect reported on very low-density lipoprotein (VLDL).

or no effect reported on very low-density ipoprotein (VLUL).
Studies on the mode of action of Lorelco indicate that it increases the fractional rate of LDL catabolism. This effect may be linked
to the observed increased excretion of fecal bile acids, a final metabolic pathway for the elimination of cholesterol from the body.
Lorelco also exhibits inhibition of early stages of cholesterol biosynthesis and slight inhibition of absorption of dietary
cholesterol. There is no increase in the cyclic precursors of cholesterol, namely desmosterol and 7-dehydrocholesterol. On this
basis, it is concluded that Lorelco does not affect the later stages of cholesterol biosynthesis.

basis, it is concluded that Lorelco does not affect the later stages of cholesterol biosynthesis.

Absorption of Lorelco from the gastrointestinal tract is limited and variable. When it is administered with food, peak blood levels are higher and less variable. With continuous administration in a dosage of 500 mg b.l.d., the blood levels of an individual gradually increase over the first three to four months and thereafter remain fairly constant. In 116 patients treated with Loreld or periods of three months to no year, the mean blood level was 23.6 ± 17.2 mcg/mt (\_ 5.8...) a ranging for 78.3 mcg/mt. Levels observed after seven years of treatment in 40 patients yielded an average value of 21.5 ± 16.5 mcg/mt. (\_ 5.8...) ranging to 78.3 mcg/mt. Levels observed after seven years of treatment in 40 patients yielded an average value of 21.5 ± 16.5 mcg/mt. (\_ 5.8...) ranging to 78.3 mcg/mt. Levels observed after seven years of treatment in 40 patients yielded an average value of 21.5 ± 16.5 mcg/mt. (\_ 5.8...) ranging to 78.3 mcg/mt. Levels observed after seven years of treatment. Six weeks after cessation of therapy, the average had fallen by 60%. After six months, the average had fallen by 80%. In Deember 1944, a National Institute of Health Consensus Development Conference Panell concluded that lowering definitely elevated blood cholesterol levels (specifically blood levels of LDL-cholesterol) will reduce the risk of heart attacks due to coronary heart disease. The effect of probucio-induced reduction of serum cholesterol of religiored levels, or mortibidity or mortality due to coronary heart disease has not been established.

HDL-cholesterol levels on morbidity or mortality due to coronary heart disease has not been established.

HDL-cholesterol levels on morbidity or mortality due to coronary heart disease has not been established.

FORTIONS AND TOXICOLOGY sections. Probucol is not an innocuous drug and strict attention should be paid to the INDICATIONS, CONTRAINDICATIONS, and WARNINGS.

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PHARMACOLOGY AND TOXICOLOGY sections. Probucol is not an innocuous drug and strict attention should be paid to the INDICATIONS. CONTRAINDICATIONS, and WARNINGS.

Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Dietary therapy specific for the type of hyperlipidemia is the initial treatment of choice. Excess body weight may be an important actor and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Contributory disease such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision ultimately is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to detail the experiment of the properties of the decision ultimately is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to detail the experiment of the properties of the decision ultimately is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to detail the experiment of a patients for cholesterol-lowering drug therapy should take into account other important coronary risk factors such as smoking, hypertension, and diabetes mellitus. Consideration should be given to the efficacy, safety, and compliance factors for each of the cholesterol-lowering drugs prior to selecting the one most appropriate for an individual patient. Loretoc may be indicated for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (Types III) and the propriate of the reduction of the patients of the propriate of the decision of the patients with combined hypercholesterolemia is the abnormality of most concern. After establishing that the elevation is the patients with combined hypercholesterolemia is the abno

When total triglycerides are greater than 400 mg/dL, this equation is less accurate. In such patients, LDL-cholesterol may be obtained by ultracentrifugation.

t is not always possible to predict from the lipoprotein type or other factors which patients will exhibit favorable results. Lipid levels, including HDL-cholesterol, should be periodically assessed.

The effect of probucol-induced reduction of serum cholesterol or triglyceride levels, or reduction of HDL-cholesterol levels or morbidity or mortality due to coronary heart disease has not been established.

morbidity or mortality due to coronary heart disease has not been established.

CONTRAINDICATIONS: (See also WARNINGS and PRECAUTIONS.) Loreico is contraindicated in patients who are known to have a hypersensitivity to it. Loreico is contraindicated in patients with evidence of recent or progressive myocardial damage or findings suggestive of serious ventricular arrhythmias or with unexplained syncope or syncope of cardiovascular origin.

Loreico is contraindicated in patients with an abnormally long OT interval.

WARNINGS: SERIOUS ANIMAL TOXICITY HAS BEEN ENCOUNTERED WITH PROBUCOL IN RHESUS MONKEYS FED AN ATHEROGENIC DIET AND IN BEAGLE DOGS. (SEE ANIMAL PHARMACDUGY AND TOXICOLOGY SECTION.)

Prolongation of the OT interval can occur in patients on Loreico. Serious arrhythmias have been seen in association with an abnormally long OT interval in patients on Loreico alone and in patients on Loreico and a concomitant antiarrhythmic drug. The following precautions are deemed pruden!

1. Patients should be advised to adhere to a low cholesterol, low fat diet at the start of treatment with Loreico and throughout the treatment period.

- An ECG should be done prior to starting treatment and repeated at appropriate intervals during treatment. If an abnormally long QT interval is observed, the possible benefits and risks should be carefully considered before making a decision to tinue Lorelco

Loreico therapy should be discontinued or not started if the QT interval at an observed heart rate on a resting ECG is persistently more than one of the values listed below:

Observed Heart Rate	QT Interval in sec (15% above the upper limit of normal)*		
(beats/min)	Males	Females	
40	0.56	0.58	
50	0.52	0.53	
60	0.49	0.50	
70	0.45	0.47	
80	0.43	0.44	
86	0.42	0.43	
92	0.40	0.41	
100	0.39	0.40	
	0.37	0.38	
109	0.36	0.36	
120	0.30	0.35	

U.34 0.35

\*Values calculated from Burch GE, Winsor T. A primer of electrocardiography. Philadelphia, PA: Lea and Febiger; 1958; p 272 (Table 6).

- 3. Patients developing unexplained syncope or syncope of cardiovascular origin should have Lorelco therapy discontinued and should have ECG surveillance.
- a. An increase in the dose of the drug.

  a. An increase in the dose of the drug.

  b. Addition of a second drug that prolongs the QT interval (including tricyclic antidepressants, class I and III antiarrhythmics, and phenothiazines).

and phenothiazines).

c. Hypokalemia or hypomagnesemia.
d. Severe bradycardia due to intrinsic heart disease or drug effects on the atrial rate (beta-blockers) or AV block (digoxin).
e. Development of recent or acute myocardial infarction, ischemia, or inflammation.

The use of Lorelco in patients receiving any of these drugs should be based on the conclusion that alternate methods of hypocholesterolemic therapy are either ineffective or not tolerated, and the potential benefits of cholesterol lowering outweigh the risk of serious arrhythmia.

The following conditions should be resolved or corrected prior to initiation of therapy with Lorelco:

due to intrinsic heart disease or drug effects on the atrial rate (beta-blockers) or AV block (digoxin) occardial infarction, ischemia, or inflammation.

c. Severe bradycarola oue to munish, users of which are to a construction of the description of the construction of the constr

Information for Patients: The patient should be instructed to adhere to a prudent diet. Females should be cautioned against becoming pregnant for at least six months after discontinuing Lorelco and should not breast-feed their infants during therapy with Lorelco.

Laboratory Tests: The physician should schedule periodic blood lipid determinations and periodic ECGs. (See WARNINGS. Laboratory Tests: the physician should schedule periodic closon lipid determinations and periodic Euclis. (See WARNINGS.). Elevations of the serum transaminases (SGOT, SGPT), bilirubin, alkaline phosphatase, creatine phosphokinase, in caid, blood urea nitrogen, and blood glucose above the normal range were observed on one or more occasions in various patients treate with Lorelco. Most often these were transient and/or could have been related to the patient's clinical state or other modes of therapy. Although the basis for the relationship between Lorelco and these abnormalities is not firm, the possibility that some of therapy are drug related cannot be excluded. In controlled trials, the incidence of abnormal laboratory values was no higher in patients treated with Lorelco than in the patients who received placebo. If abnormal laboratory tests persist or worsen, if clinical signs consistent with the abnormal laboratory tests develop, or if systemic manifestations occur, Lorelco should be discontinued.

eractions: The addition of clofibrate to Lorelco is not recommended, since the lowering effect on mean serun .DL or total cholesterol is generally not significantly additive and, in some patients, there may be a pron

Neither or all hypoglycemic agents nor oral anticoagulants alter the effect of Lorelco on serum cholesterol. The dosage of the agents is not usually modified when given with Lorelco.

agents is not usually modified when given with Lorelco.

Monkeys fed a high fat, high cholesterol diet admixed with probucol exhibited serious toxicity. (See WARNINGS and ANIMA)
PHARMACOLOGY AND TOXICOLOGY sections.) Prolongation of the UT interval can occur in patients on Lorelco and serious
arrhythmias have been seen in association with an abnormally long UT interval in patients on Lorelco. The addition of a second
drug that prolongs the OT interval (including throughcast and III antiarrhythmics, and phenothiazines) may
increase the risk of serious arrhythmia. (See CONTRAINDICATIONS AND WARNINGS.)

Carcinogenesis, Mutagenesis, Impairment of Fertility
In chronic studies of two years' duration in rats, no loxicity or carcinogenicity was observed. These results are consistent with
the lack of any adverse effect on fertility and the negative findings in tests for mutagenic activity in rats.

Pregnancy Teratogenic Effects Pregnancy—Categor dose, and have revea Teratogenic Effects
Pregnancy—Category B: Reproduction studies have been performed in rats and rabbits at doses up to 50 times the humat dose, and have revealed no evidence of impaired ferbility or harm to the fetus due to probucol. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Furthermore, if a patient wishes to become pregnant, it is recommended that the drug be withdrawn and birth control procedures be used for at least six months because of persistence of the drug in the body for prolonged periods. (See CLINICAL PHARMACOLOGY.)

persistence of the drug in the dody of provinged persons does determine the delivery is unknown.

Labor And Delivery: The effect of Loreloo on human labor and delivery is unknown.

Nursing Mothers: It is not known whether this drug is excreted in human milk, but it is likely, since such excretion has beet shown in animals. It is recommended that nursing not be undertaken white a patient is on Loreloo.

Pediatric Use: Safety and effectiveness in children have not been established

ADVERSE REACTIONS
Gastrointestinal

se stools, flatulence, abdominal pain, nausea, vomiting, indigestion, gastrointestinal bleeding diarrhea or loos Cardiovascular

ardiovascular prolongation of the QT interval on ECG, syncope, ventricular arrhythmias (ventricular tachycardia, torsades de pointes ventricular fibrillation), sudden death

Neurologic headache, dizziness, paresthesia, insomnia, tinnitus, peripheral neuritis

natologic osinophilia, low hemoglobin and/or hematocrit, thrombocytopenia

**Dermatologic** rash, pruritus, ecchymosis, petechiae, hyperhidrosis, fetid sweat

Genitourinary

impotency, nocturia

Ophthalmic
conjunctivitis, tearing, blurred vision

Endocrine enlargement of multinodular goiter

**isies** I with initiation of therapy and characterized by dizziness, palpitations, syncope, nausea, vomiting and chest pai

Other diminished sense of taste and smell, anorexia, angioneurotic edema 
DRUG ABUSE AND DEPENDENCE: No evidence of abuse potential has been associated with Lorelco, nor is there 
evidence of psychological or polysical dependence in humans.

evidence of psychological or physical dependence in humans

OVERDOSAGE: There is a single report of a 15-kg, three-year-old, male child who ingested 5 g of probucol. Emesis was

OVERDOSAGE: There is a single report of a 15-kg, three-year-old, male child who ingested 5 g of probucol. For induced by piecea. The child remained well, apart from a brief episode of loose stools and flatulence. No specific information is available on the treatment of overdosage with Loretoo and no specific antioties is available. Probucol is not dialyzable freatment is symptomatic and supportive. Probucol has shown no identifiable acute toxicity in mice and rats. In these animals the LD<sub>0</sub> (oral) is in excess of 5 g/kg of body weight.

DOSAGE AND ADMINISTRATION: For adult use only. The recommended and maximal dose is 1000 mg daily given in two divided doses of 500 mg each (two 250 mg tablets or one 500 mg tablet) with the morning and evening meals.

HOW SUPPLIED: 250 mg round, white, film-coated tablets imprinted with either the DOW diamond trademark over th code number 51 or LORELCO 250. Bottles of 120 (NDC 0068-0051-52)

500 mg capsule-shaped, white, film-coated tablets, marked LORELCO 500. Bottles of 100 (NDC 0068-0053-61) Keep well closed. Store in a dry place. Avoid excessive heat. Dispense in well-closed light-resistant containers with child resistant closure.

keep well closed. Store in a dry place. Avoid excessive heat: Uispense in weil-closed light-resistant containers with cresistant closure.

ANIMAL PHARMACOLOGY AND TOXICOLOGY: In rhesus monkeys, administration of probucol in diets containing unusually high amounts of cholesterol and saturated fat resulted in the death of four of eight animals after several weeks Premonitory syncope was frequently observed and was associated with a pronounced prolongation of the OT intervals (30 to 50% longer than that observed in untreated monkeys). Serum levels of probucol greater fran 20 mcg/mt associated with some prolongation in the OT interval in the cholesterol-led monkey. A 75 msec or greater increase in OT interval from control values was usually seen at 40 mcg/mt. and above, Blood levels in humans receiving probucol three to thirty times the human dose equivalent achieved blood levels only one-third those approximatel 20 mcg/mt. and not uncommonly reach levels of 40 mcg/mt. and higher. Rhesus monkeys fed normal (low fat) chow an exceiving probucol three to thirty times the human dose equivalent achieved blood levels only one-third those of many human subjects. No adverse effects were detected in these monkeys over an eight-year period of continuous drug administration, it another study in rhesus monkeys, an atherogenic clied was set for two years and daily treatment with probucol, separated in time from the atherogenic meal, was carried out during the second year. Serum probucol levels ranged 20 to 50 mcg/mt. In fived 1 monkeys, and less in the remaining animals. Marked prolongation of the OT, interval in the ECG or syncopal behavior was never observed over the entire one-year treatment period. Regression of gross aortic lesions comparable to that observed in a paraset of the many days. Among a 2 probucol-toxelety anime was seen in animals receiving probucol It should be emphasized that both HDL cholesterol and EDL-cholesterol were markedly reduced in this regression study. During the performance of a two-year chromstud

injections of epinephrine to probucol-treated monkeys did not induce ventricular fibrillation.

In other studies, monkeys were given probuool either before and after, or only after myocardial infarction was induced by coronary artery liqation. In these studies, there was no difference between probucol- and placebo-treated groups with respect to either survival or detailed blind quantitation of myocardial changes (gross and histopathologic). Probucol has shown no identifiable toxicity in mice and rats. In these animals, the LDsg (oral) is in excess of 5 g/kg of bod weight. In chronic estudies of two years' duration in rats, no toxicity or carcinogenicity was observed. From studies in rats, dogs, and monkeys, it is known that probucol accumulates slowly in adipose tissue. Approximately 90% o probucol administered orally is unabsorbed. For that which is absorbed, the biliary tract is the major pathway for clearance from the body and very little is excreted by way of the kidneys.

Myocardial injury was produced in various groups of rats by one of the following procedures: aortic coarctation, complete in the probucol administration, no deleterous effects related to treatment occurrer as measured by survival and microscopic examination of myocardial damage.

Probuool was administered to miningips beginning ten days before ligation of coronary artery and continued for 60 days after the probused was administered to miningips beginning to endow before ligation of coronary artery and continued for 60 days after the probused was administered to miningips beginning the days before ligation of coronary artery and continued for 60 days after the probused was administered to mining a beginning the days before ligation of coronary artery and continued for 60 days after the probused was administered to mining a second and the probused was administered to mining a beginning to the probused was administered to mining a second and the probused was administered to mining a despiration of coronary artery and continued for 60 days af

Probucol was administered to minipigs beginning ten days before ligation of coronary artery and continued for 60 days afte surgery. Challenge with epinephrine at the end of 60 days tailed to induce ventricular fibrillation in any of the coronary-ligated probucol-treated minipigs.

probucol-treated minipigs

CLINCAL STUDIES: In a multicenter, randomized, double-blind study, the LRC-CPPT.3 hypercholesterolemic patient
treated with an oral bite acid sequestrant (cholestyramine) and a cholesterol-inwering diet experienced average total and LDL
noisesterol reductions greater than those obtained in the placebo group treated with det alone. The cumulous even-yea
incidence of the primary end point—combined incidence of definite CHD death and/or definite nontatal myocardial infarction—
was 7% in the cholestyramine group and 8.6% in the placebo group. This was a 19% reduction in risk (Plest no 0.5 single
tail test) of the primary end point reflecting a 24% reduction in definite CHD death and a 19% reduction in nonfatal myocardia
infarction.

The subjects included in the study were middle-aged men (35-59 years old) with serum cholesterol levels at least 265 mg/dL and no previous history of heart disease. It is not clear to what extent these findings can be extrapolated to other segments of the hypercholesterolemic population not studied.

The bile acid sequestant, cholestyramine, was used in the above trial. Caution should be exercised in extrapolating these result to Lorelos since it differs from cholestyramine with regard to its mode of action, spectrum of cholesterol-lowering potency effect on HDL-cholesterol. and possible toxicity. The effect of probucol-induced reduction of serum cholesterol levels or morbidity or mortality due to coronary heart disease has not been established.

Consensus Development Panel. Lowering blood cholesterol to prevent heart disease. JAMA. 1985; 253:2080-2086. Fredrickson DS, Levy RI, Lees RS. Fat transport in lipoproteins—an integrated approach to mechanisms and disorders. Engl J Med. 1967; 276:34-44. The Lipid Research Clinics Program. The Lipid Research Clinics coronary primary prevention trial results: I. Reduction incidence of coronary heart disease. JAMA. 1984; 251:351-364. Y342

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abnormal resting Doppler E/A ratio become normal. Although head-up positioning diminished the E/A ratio in normal subjects, it did not become abnormal. Alterations of LV loading conditions alter the pattern of LV filling, whether normal or abnormal at baseline. The magnitude of change seen appears to be independent of the resting pattern of flow. Simple changes in venous return do not "normalize" an abnormal pattern, nor do they "abnormalize" a normal pattern.

#### **METHODS**

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**Accuracy of Digital Holter Monitoring of Extent and Duration** of Ischemic Episodes Compared to Analog Recording

Sigmund Silber, Ravi K. Bajaj, Katharine A. Kirk, and Gerald M. Pohost

Newly developed digital Holter devices may be more reliable for STsegment analysis. We compared the results of digital 2-channel ST-segment analysis directly to those of analog amplitude-modulated recordings in identical leads. Thirty-five patients underwent graded treadmill exercise testing. For digital analysis, the correlation coefficient for CM5 was 0.97 and for CM<sub>3</sub> it was 0.93. For analog recording, the correlation coefficient for CM<sub>5</sub> was 0.88 and for CM<sub>3</sub> it was 0.85. Regarding the duration of ischemic episodes, digital Holter showed a significantly better agreement (r = 0.97) than analog Holter (r = 0.84). Because analog amplitude-modulated Holter recordings overestimated the degree and duration of ischemic episodes, digital devices should be used to assess myocardial ischemia during ambulatory conditions.

#### **BRIEF REPORTS**

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**Mechanism of Directed Transluminal Atherectomy** 

Danna E. Johnson, Lissa Braden, and John B. Simpson

Reproducibility and Circadian Rhythm of Heart Rate Variability in Healthy Subjects

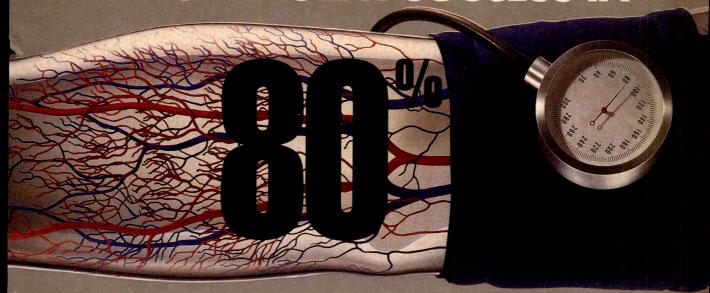
Heikki V. Huikuri, Kenneth M. Kessler, Elisabeth Terracall, Agustin Castellanos, Markku K. Linnaluoto, and Robert J. Myerburg

Utility of a Stimulus Artifact Suppressor for Transesophageal **Pacing** 

D. Woodrow Benson Jr., Hossein Jadvar, and Janette F. Strasburger

Continued on page A50

# SINGLE-AGENT SUCCESS IN



# OF HYPERTENSIVE PATIENTS\*\*\*

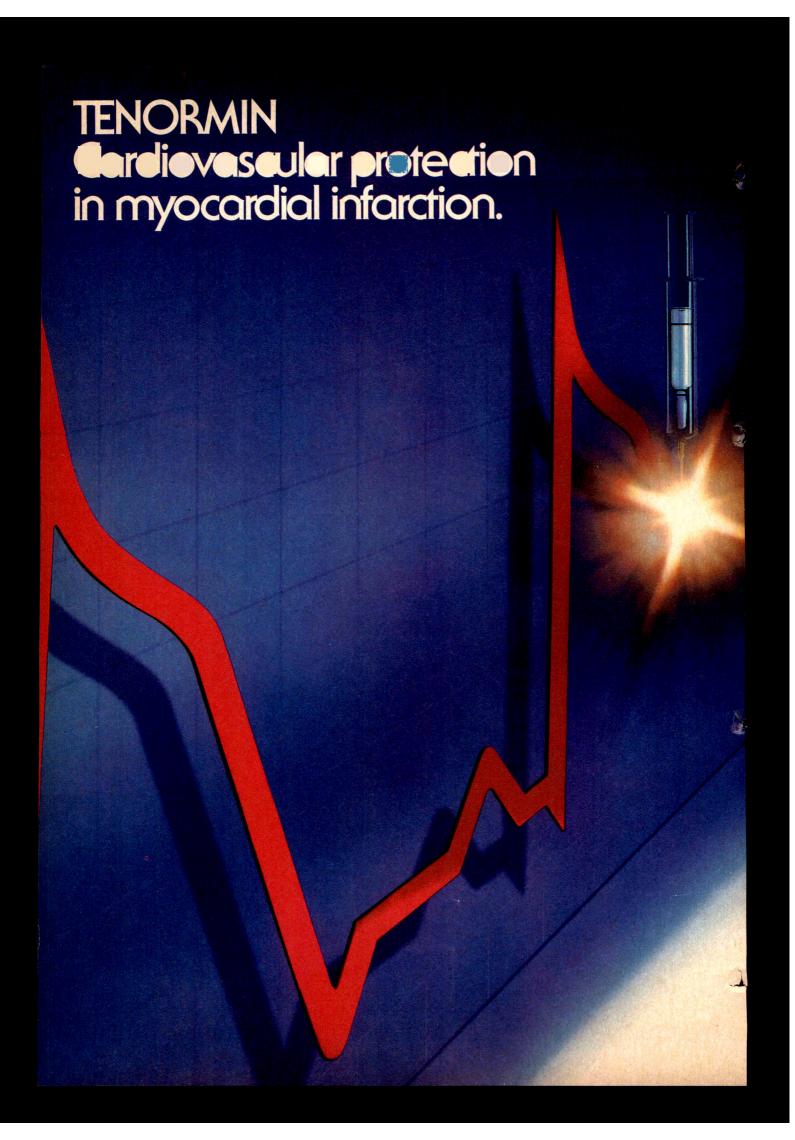


SEARLE Searle & Co. San Juan, PR 00936

395
Lack of Sustained Hemodynamic Effects of the Beta <sub>2</sub> - Adrenoceptor Agonist Dopexamine in End-Stage Congestive
Heart Failure
Michael Böhm, Elisabeth Reuschel-Janetschek, and Erland Erdmann
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The Complex of Myxomas, Pigmentation and Endocrine
Overactivity
Wesley S. Bennett, Thomas N. Skelton, and Patrick H. Lehan

**INSTRUCTIONS TO AUTHORS on page A91** 

Now— A new life-saving regimen.



# New

# TENORMIN I.V. followed by TENORMIN Tablet

# Increased survival in a 16,000-patient study.

In the ISIS-1 trial—"Randomised Trial of Intravenous Atenolol Among 16,027 Cases of Suspected Acute Myocardial Infarction"— in patients randomized within 12 hours of symptom onset, the TENORMIN Regimen reduced MI mortality by 30% at day one and maintained a significant reduction throughout a year of follow-up. When patients were randomized within 2 hours of the onset of pain, first-week mortality was reduced by 53%.1

Significantly Reduced Mortality After MI\*

	Day One	Week One	Year One
*Adapted from ISIS-1 study.¹ ¹Data derived.	30%	15%	11%
Control-group deaths	171/7,990	365/7,990	923/7,930
TENORMIN-group de	eaths 121/8,037	313/8,037	825/7,968
	2P<.003 <sup>+</sup>	2P < .04	2P < .01

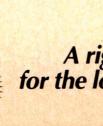
Good clinical judgment suggests that patients who are dependent on sympathetic stimulation for adequate cardiac output and BP are not good candidates for beta blockade. In addition to patients excluded from the ISIS-1 study, those with borderline BP (ie, systolic < 120, especially if over age 60) are less likely to benefit.

# Provides cardiovascular protection...

A second major study—"Reduction of Infarct Size, Arrhythmias and Chest Pain by Early Intravenous Beta Blockade in Suspected Acute Myocardial Infarction " showed that the TENORMIN Regimen reduced enzyme elevation and sudden death while also reducing chest pain and frequency of ventricular premature beats.2

# ...with uncompromised safety.

Compared to controls, patients on the TENORMIN Regimen had less need for antifailure, antiarrhythmic, and antianginal therapy.<sup>2</sup> In fact, TENORMIN reduced signs of heart failure and cardiogenic shock, and it reduced R-on-T ectopies by 61% (2P < .0001).2



A right start for the long run. I.V. INJECTION/TABLETS (atenolo

See last page for brief summary of prescribing information.

# A right start for the long run. ENORMIN (atenolol)

INDICATIONS AND USAGE: Hypertension: TENORMIN is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type duretic.

Angina Pectorios Due to Coronary Atherosclerosis: TENORMIN is indicated for the long-term management of patients with

Acute Myocardial Infarction: TENORMIN is indicated in the management of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment can be initiated as soon as the patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment can be initiated as soon as the patients continued in the patients with soon as the patients with solid patients like those who were excluded from the ISIS-1 trial (blood pressure less than 100 mm Hg systolic, heart rate less than 50 pm) or have other reasons to avoid beta blookade. As noted above, some subgroups (eg. efterly patients with systolic blood pressure below 120 mm Hg) seemed less likely to benefit.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. (See WARNINGS.)

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and denoted slow AV conduction.

In patients with acute myocardial infarction, cardiac failure which is not promptly and effectively controlled by 80 mg of intravenous furosemide or gouvinent therapy is a contraindication to beta-blocker treatment.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, apaents of the period of time can in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, apaents of the period of time can in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, abeliants sho Acute Myocardial Infarction: TENORMIN is indicated in the management of hemodynamically stable patients with definite or

Cessation of Therapy With TENORMIN: Patients with coronary artery disease, who are being treated with TENORMIN, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with other beta blockers. The last two complications may occur with or without preceding exacerbation of the angina petcriots. To deep there has been no report of myocardial infarction or severe angina upon withdrawal of TENORMIN, probably due to its long plasma half-life. Because of the problems encountered with other beta blockers, when discontinuation of TENORMIN is planned, the petients should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that TENORMIN be promptly reinstituted, at least temporarily. (See DOSAGE AND ADMINISTRATION.)

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is not absolute, the lowest possible dose of TENORMIN should be used with therapy initiated at 50 mg and a beta, stimulatin agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels

order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium such as either, cyclopropane, and richloroethylene.

Additionally, caution should be used when TENORMIN I.V. Injection is administered concomitantly with such agents. TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents: eg, dobutamine or isoproterenol with caution (see section on OVERDOSAGE). Manifestations of excessive vagal tone (eg, protound bradycardia, hypotension) may be corrected with atropine (1-2 mg IV).

Diabetes and Hypodycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking against is required. Beta blockers may mask tachycardia occurring with hypodycemia, but other manifestations such as dizzness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood discose to normal levels.

significantly affected. IEN/HMM obes not potentiate insulin-induced rybodycemia and, unline nonselective deal audoces, or delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Patients suspected of having thyroid disease should be monitored closely when administering TENCRMIN I.V. Injection. Abrout withdra beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENOR therapy is to be withdrawn should be monitored closely. (See DOSAGE AND ADMINISTRATION.)

PERCAUTIONS: General: Patients already on a beta blocker must be evaluated carefully before TENORMIN is administered and subsequent TENORMIN dosages can be adjusted downward depending on clinical observations including pulse and blood

Impaired Renal Function: The drug should be used with caution in patients with impaired renal function. (See DOSAGE AND ADMINISTRATION.)

MINISTATION.)

Thus interactions: Catecholamine-depleting drugs (eg. reserpine) may have an additive effect when given with beta-blocking ents. Patients treated with TENORIMIN plus a catecholamine depletor should therefore be closely observed for evidence of potension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should

be discontinued several days before the gradual withdrawal of clonidine.

Caution should be exercised with TENORIMIN I.V. Injection when given in close proximity with drugs that may also depressant effect on myocardial contractility. On rare occasions, concenitant use of intravenous beta blockers and intravenous vera pamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure, or recent

myocardial infarction.

Information on concurrent usage of atenolol and aspirin is limited. Data from several studies, ie, TIMI-II, ISIS-2, currently do not suggest any clinical interaction between aspirin and beta blockers in the acute myocardial infarction setting.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 in bomoths) mouse study, each employing oral dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human antihypertensive dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this findian.

Fertility of male or temale rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended numan anthyperfansive doses) was unaffected by atenoid administration.

Animal Toxicology: Chronic studies employing oral atenoid performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenoid (starting at 15 mg/kg/day or 7.5 times the maximum recommended human antihyperfensive dose) and increased incidence of atrial degeneration of hearts of male rats at 300 but not 150 mg atenoid/kg/day (150 and 75 times the maximum recommended human antihyperfensive

is, respectively). Usage in Pregnancy: Pregnancy Category C: Atendol has been shown to produce a dose-related increase in embryofietal orptions in rats at doses equal to or greater than 50 mg/kg/gay or 25 or more times the maximum recommended human antihytensive dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above mg/kg/gay or 125 times the maximum recommended human antihyperensive dose. There are no adequate and well-controlled dies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the

fetus.

Based on a 50 kg patient weight.

Nursing Mothers: Aleroido is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared to the concentration in plasma.

Caution should be exercised when TENORIMIN is administered to a nursing woman.

Pediatric Use: Sately and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in hyperensive patients in which adverse reactions were either volunteered by the patient (US studies) or elicited, eg, by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects of TENORMIN and placebo is similar, causal relationship to TENORMIN is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the US studies (volunteered and effects):

effects) and then from both US and foreign studies (volunteered and elicited side effects)
US STUDIES (ATENOLOL, n=164; PLACEBO, n=206) (% ATENOLOL-% PLACEBO):

US STUDIES (ATEMOLOL, ns164; PLACEBO, ns208) (% ATEMOLOL-% PLACEBO);
CARDIOVASCULAR: bradycaria (3%-0%), cold extremites (0%-0.5%), bostural hypotension (2%-1%), leg pain (0%-0.5%)
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), latigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0.5%), depression (0.6%-0.5%), dreaming (0%-0.5%)
ASTROINTESTINAL: diarrhes (2%-0%), nausea (4%-1%), depression (0.6%-0.5%), dreaming (0%-0.5%)
RESPIRATORY (see WARNINGS); wheeziness (0%-0%), dyspnea (0.5%-1%), postural hypotension (4%-5%), leg pain (3%-1%)
CARDIOVASCULAR: bradycarda (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dzizzness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%)
RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%)
In a series of investigations in the treatment of acute myocardial infarction, bradycardia and hypotension occurred more commonly,
as expected for any beta blocker, in atenolol-treated patients than in control patients. However, these usually responded to atropine and/
or to withholding further dosage of atenolol. The incidence of heart failure was not increased by atenolol. Inotropic agents were infrequently used. The reported frequency of these and other events occurring during these investigations is given below.
In a study of 477 patients, the following adverse events were reported during either intravenous andro or all atenolol administration:
CONVENTIONAL THERAPY PLUS ATENOLOL (n=244): bradycardia, 43 (15%); hypotension, 50 (25%); bronchospasm, 3 (12%);
heart failure, 46 (19%); heart fallure, 4 (1.6%); ventricular tachycardia, 28 (1.5%); series, and a created a create, 4 (1.6%); deaths, 7 (2.9%); cardiogenic shock, 1 (0.4%); development of ventricular septacles (1.0%);
development of mitral regurgitation, 0 (0%); renal failure, 1 (0.4%); pulmonary emboli, 3 (1.2%);
development of mitral regurgitation, 0 (0%); renal failure, 4 (10%); pulmonary emboli, 3 (1.2%);
CONVENTIONAL THERAPY ALONE (n=233): bradycardia, 24 (10%); hypotension, 34 (15%); bronchospasm, 2 (0.9%); heart
failure, 56 (24%); heart block, 10 (4.3%); BBB + major axis deviation, 26 (12%); supraventricular tachycardia, 45 (19%); hypotension, 6 (2.6%); chiralitation, 6 (6.9%); chiralitation

the following reasons:
REASONS FOR REDUCED DOSAGE

REASONS FOR REDUCED DOSAGE

17 ATENOLOL' REDUCED DOSA (5 mg): hypotension/bradycardia, 105 (1.3%); cardiogenic shock, 4 (.04%); reinfarction, 0 (0%); cardiac arrest, 5 (.06%); heart DloSE (5 mg): hypotension/bradycardia, 105 (1.3%); cardiogenic shock, 3 (.04%); bronchospasm, 1 (.01%) ORAL PARTIAL DOSE: hypotension/bradycardia, 1168 (14.5%); cardiogenic shock, 35 (.44%); reinfarction, 5 (.05%); cárdiac arrest, 82 (.34%); hard block (5 lirst degree), 134 (1.7%); cardiac failure, 233 (2.9%); arrhythmias, 22 (.27%); bronchospasm, 50 (.62%)

\*Full dosage was 10 mg and some patients received less than 10 mg but more than 5 mg
POTENTIAL ADVENSE EFFECTS: In addition, a variety of adversee effects have been reported with other beta-adrenergic blockling agents, and may be considered potential adverse effects of TENORIMIN.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Fever, combined with aching and sore throat, larynospasm, and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation of time and place; short-term memory loss; emotional lability with slightly clouded sensorium; and, decreased performance on neuropsychometrics.

sorium; and, decreased performance on neuropsychometrics

sensorium; and, decreased performance on neuropsychometrics.

Gastrointestinal: Mesentenic arterial thromboss, sichemic colitis.

Other: Reversible alopecia, Peryonie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small, and in most cases, the symptomes have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy. (Seo DOSAGE AND DAMINISTRATION.)

The occulomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMINI during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMINI therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

overtousage a arraisate; the first control effects of such as a first process of a class and such as a first process. The case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodalysis. In addition to gastric lavage, the following therapeutic measures are suggested if

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BHONCHUSPASM. Ammophysites, superseries, via any processor, and the processor of the proces ely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine,

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Angina Pectoris: The initial dose of TENORMIN is 50 mg given as one tablet a day. If an optimal response is not achieved within one week, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Some patients may require a dosage of 200 mg once a day for optimal effect.

Twenty-four hour control with once daily dosing is achieved by giving doses larger than necessary to achieve an immediate maximum early effect on exercise tolerance occurs with doses of 50 to 100 mg, but at these doses the effect at 24 hours is attenuated, averaging about 50% to 75% of that observed with once a day oral doses of 200 mg.

Acute Myocardial Infarction: In patients with definite or suspected acute myocardial infarction, treatment with TENORMIN I.V. Injection should be initiated in a coronary care or similar unit immediately after the patient's hemographyamic conditions at stabilized. Treatment should begin with the intravenous administration of 5 mg TENORMIN over 5 minutes followed by another 5 mg intravenous injection 10 minutes later. TENORMIN I.V. Injections insolud be administrated under carefully controlled conditions including monitoring of lolod pressure, heart rate, and electrocardiogram. Dilutions of TENORMIN I.V. injection in Dexrose injection USP, Sodium Chloride and Dextrose injection may be used. These admixtures are stable for 48 hours if they are not used immediately.

immediately.

In patients who tolerate the full intravenous dose (10 mg), TENORMIN Tablets 50 mg should be initiated 10 minutes a fler the last intravenous dose followed by another 50 mg oral dose 12 hours later. Thereafter, TENORMIN can be given orally either 100 mg once daily or 50 mg twice a day for a further 6-9 days or until discharge from the hospital. If bradycardia or hypotension requiring treatment or any other untoward effects occur, TENORMIN should be discontinued. (See full prescribing information prior to initiating therapy with TENORMIN Tablets).

Data from other beta blocker trials suggest that if there is any question concerning the use of IV beta blocker or clinical estimate that there is a contraindication, the IV beta blocker may be eliminated and patients fulfilling the safety criteria may be given TENORMIN Tablets 50 mg twice daily or 100 mg once a day for at least seven days (if the IV dosing is excluded).

Although the demonstration of efficacy of TENORMIN is based entirely on data from the first seven postinifaction days, data from other beta blocker trials suggest that treatment with beta blockers that are effective in the postinifaction setting may be continued for one to tree years if there are no contraindications.

TENORMIN is an additional treatment to standard coronary care unit therapor.

TENORMIN is an additional treatment to standard coronary care unit therapy.

Patients With Renal Impairment: Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 mL/min/1.73 m²/(normal range is 100-150 mL/min/1.73 m²/); therefore, the following maximum oral dosages are recommended for patients with renal

Creatinine Clearance (mL/min/1.73 m²)	Elimination Half-Life (h)	Maximum Dosage
15-35	16-27 >27	50 mg daily 50 mg every other da

Patients on hemodialysis should be given 50 mg after each dialysis; this should be done under hospital supervision as marked falls in Clessation of Therapy in Patients With Angina Pectoris: If withdrawal of TENORMIN therapy is planned, it should be achieved gradually, and patients should be carefully observed and advised to limit physical activity to a minimum.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Rev H 8/89

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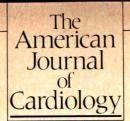
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# Frequency and Importance of Silent Myocardial Ischemia Identified with Ambulatory Electrocardiographic Monitoring in the Early In-Hospital Period After Acute Myocardial Infarction

Pamela Ouyang, MD, Nisha Chibber Chandra, MD, and Sidney O. Gottlieb, MD

The incidence and clinical significance of silent myocardial ischemia occurring in the early period after acute myocardial infarction (AMI) was studied in 59 patients who had an uncomplicated early course after admission for AMI. Calibrated 2-lead ambulatory electrocardiographic monitoring performed for 39  $\pm$  2 hours starting 4  $\pm$  1 days after AMI identified silent myocardial ischemia, defined as ≥1 mm ST-segment change lasting ≥2 minutes, in 27 patients. These patients had  $5 \pm 1$  episodes lasting a median of 11 minutes/episode (range 2 to 36 minutes/episode). Patients with and without silent ischemia had comparable baseline demographics, were receiving similar antiischemic medications and had similar severity of coronary disease by angiography. No reinfarctions occurred during the inhospital period. Fourteen of 27 patients (52%) with silent ischemia had ≥1 in-hospital clinical ischemic event (pulmonary edema, n = 5, cardiac death, n = 1, and postinfarction angina, n = 11). In contrast, only 7 of 32 patients without silent ischemia (22%) had  $\geq 1$  in-hospital event (pulmonary edema, n = 1, cardiac death, n = 1, and postinfarction angina, n = 6). The frequency of ischemic events was significantly greater in patients with silent ischemia compared to those without silent ischemia, p <0.02. Silent ischemia occurs frequently very early after AMI and identifies a group of patients who are at increased risk for adverse in-hospital clinical outcomes.

(Am J Cardiol 1990;65:267-270)

cute myocardial infarction (AMI) affects approximately 1 million Americans each year. Despite therapeutic strategies designed to limit infarct size and to reduce early mortality in selected groups of patients treated early after onset of symptoms, the overall 1-year mortality after AMI remains in excess of 10%. Risk stratification after postinfarction based on clinical course, left ventricular function, severity of arrhythmias and exercise testing identifies patients at high and low risk of subsequent ischemic events.1-8 In addition to spontaneous and exercise-induced postinfarction angina, ischemia on predischarge exercise treadmill testing identifies patients with a significantly increased 1-year mortality.3 However, some patients cannot perform treadmill testing because of musculoskeletal abnormalities, congestive heart failure or arrhythmias. Alternative methods for identifying recurrent ischemia would therefore be useful.

Ambulatory electrocardiographic monitoring has been used extensively to identify arrhythmias and more recently to identify transient, often asymptomatic, episodes of ST-segment changes indicative of ischemia.9-11 Episodes of transient ST-segment depression have been correlated with other more direct indexes of myocardial ischemia in patients with known coronary artery disease. 12,13 Asymptomatic myocardial ischemia occurs frequently in patients with unstable angina and is correlated with cardiovascular morbidity and mortality. 13-16 Also, ischemic ST change on predischarge ambulatory monitoring has been shown to be an important predictor of mortality in a group of high-risk postinfarction patients with low ejection fraction and high Lown grade arrhythmias.<sup>17</sup> Ambulatory electrocardiographic monitoring performed months to years after AMI has also been reported to predict subsequent cardiac events. 18 The aim of this prospective study was to determine the frequency of silent ischemia on ambulatory electrocardiographic monitoring during the very early in-hospital period after AMI and to determine whether its presence predicts subsequent overt ischemic episodes during the in-hospital period.

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**TABLE I AECG Results** ST Changes No ST Changes (n = 27)(n = 32)Duration of AECG (hrs)  $40 \pm 2$  $38 \pm 2$ No. of ST depression  $5 \pm 1$ 0 episodes Total duration (min) Median 68 0 Range 2-394 Duration/episodes (min) Median 2-36 0 Average HR at onset of  $83 \pm 3$ NA ST depression episodes (beats/min)

AECG = ambulatory electrocardiographic monitoring; HR = heart rate; NA =

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Patient population: One hundred one consecutive patients admitted to the coronary care unit with a diagnosis of AMI, either Q-wave or non-Q-wave, between October 1986 and January 1988, were evaluated for ambulatory electrocardiographic monitoring. Patients were excluded because of left bundle branch block, other intraventricular conduction abnormalities, left ventricular hypertrophy or persistent marked ST abnormalities on the 12-lead electrocardiogram on day 2 (15), or because their hospital course was unstable over the first 24 to 48 hours after admission (15). Patients were considered unstable if they had angina after infarction, required pressor support or were in Killip class III. Twelve patients were not approached for participation in the study because of logistic reasons. The remaining 59 patients who met entry criteria had electrocardiographic monitoring for 48 hours starting 3 to 5 days after admission. Myocardial infarction was confirmed by an increase in creatine kinase to >2 times normal with an associated increase in MB isoenzyme to >4% of total creatine kinase. Results of the ambulatory electrocardiographic monitoring were not disclosed to the attending cardiologist. The in-hospital clinical course was prospectively evaluated. Forty-two of 59 patients (71%) underwent cardiac catheterization within 1 month of the AMI. Outcome variables evaluated included symptomatic ischemic episodes; these were defined as cardiac death, reinfarction, recurrent episodes of pulmonary edema occurring >72 hours after admission and felt by the clinical cardiologist to represent transient myocardial ischemia, and angina after infarction.

Ambulatory electrocardiographic monitoring: Patients were monitored 3 to 5 days after hospital admission using a calibrated amplitude-modulated reel-to-reel 2-channel monitor system. Most patients were restricted to limited levels of activity, including sitting in the chair or walking within the hospital room. The leads monitored were either those showing evidence of transient electrocardiographic changes at the time of hospital admission or leads representing a modified inferior (lead II, III or aVF) and a modified precordial lead (V4, V5 or V<sub>6</sub>) that did not have significant baseline ST-segment abnormalities. All tapes were scanned by 1 techni-

No. of Pts	ST Changes (n = 27)	No ST Changes (n = 32)
Age (yrs)	60 ± 3	61 ± 6
Peak CPK (IU)	$1,292 \pm 193$	$1,940 \pm 316$
Male sex (%)	20 (74)	23 (72)
Prior AMI (%)	7 (26)	9 (28)
Cigarette use (%)	17 (63)	19 (59)
Systemic hypertension (%)	15 (56)	11 (34)
Diabetes (%)	7 (26)	6 (19)
Anterior MI (%)	12 (44)	15 (47)
Q-wave MI (%)	14 (52)	17 (53)
Thrombolytic drug (%)	3(11)	6 (19)

cian experienced in scanning for ischemic changes, who noted the time of onset and offset of each episode of ST change, printing the onset, maximum ST change and termination of each episode on paper. The results were analyzed by 2 investigators, who were blinded to patient identity and clinical course, for the number and duration of ischemic episodes, defined as ≥1 mm ST-segment depression or ≥2 mm ST elevation from baseline measured 0.08 second after the J point and lasting for 2 minutes. Elevation of the ST segment on ambulatory electrocardiographic monitoring was considered to represent ischemia if the patient had no previous Q-wave AMI. An interval of ≥2 minutes was required after the return of the ST segment to baseline before another discrete episode was counted. Each episode was determined to be either symptomatic or silent by careful review of the patient's chart.

Data analysis: Continuous variables were analyzed using unpaired t tests of significance and categorical data were analyzed using chi-square or Fisher exact tests as appropriate. Results are expressed as mean ± standard error where appropriate.

#### RESULTS

Ambulatory electrocardiographic findings: Ambulatory electrocardiographic monitoring was performed for 39  $\pm$  2 hours, starting 4  $\pm$  0.1 days after admission. The results are listed in Table I. Ischemic episodes, all of which were asymptomatic, were present in 27 of 59 patients (46%) (group 1), and absent in 32 patients (group 2). All episodes were associated with ST depression except for 2 patients with non-Q-wave AMI who had episodes of ST elevation during ambulatory electrocardiographic monitoring. The 27 patients with silent ischemia had  $5 \pm 1$  episodes lasting a median total duration of 68 minutes (range 2 to 394). The median duration/episode was 11 minutes (range 2 to 36 minutes/ episode). Fourteen patients had >60 total minutes of silent ischemia. The mean heart rate at onset of ischemia was 83 ± 3 beats/min. No patient had symptomatic ischemia during the monitoring period.

Baseline characteristics: The patients' baseline clinical characteristics are listed in Table II. Their mean age was  $61 \pm 2$  years and 73% were men. Thirty-one

**TABLE III** Medical Therapy During Ambulatory Electrocardiographic Monitoring

No. of patients (%)	ST Changes (n = 27)	No ST Changes (n = 32)
Nitrates	18 (66)	14 (44)
β blockers	7 (26)	11 (34)
Calcium antagonists	9 (33)	17 (53)
Antiplatelet drugs	2(7)	6 (19)
Heparin	11 (49)	17 (53)

patients had Q-wave AMI and 27 patients were considered to have anterior AMI based on electrocardiographic findings. Patients with or without silent ischemia on ambulatory electrocardiographic monitoring had similar clinical characteristics, risk factors and frequency of anterior and Q-wave AMIs. The number of patients who received thrombolytic agents was similar in the 2 groups. The low number of patients receiving thrombolytic treatment reflected the inclusion in this study of patients who presented to the coronary care unit beyond 4 hours after AMI, patients with non-Q-wave AMI and patients in whom thrombolytic therapy was contraindicated. A similar frequency of use of antianginal agents was also found in the groups (Table III). All patients were clinically stable before and during continuous electrocardiographic monitoring without symptomatic anginal episodes before or during the time of monitoring.

Cardiac catheterization results: Cardiac catheterization was performed within 1 month of AMI in 42 of 59 patients (71%), 18 in group 1 and 23 in group 2. The 2 groups had similar severity of coronary disease with 2 ± 0.2 arteries with >70% stenosis in both groups. Among 18 group 1 patients, 9 had 1-vessel, 3 had 2-vessel and 6 had 3-vessel disease. Among 23 group 2 patients, 11 had 1-vessel, 9 had 2-vessel and 3 had 3-vessel disease.

Clinical outcomes: Ischemic outcomes were defined as death, recurrent AMI, transient episodes of pulmonary edema that occurred later than 72 hours after hospital admission or postinfarction angina occurring before hospital discharge. Several patients experienced >1 defined outcome variable (Table IV). Among patients with silent ischemia, 14 (52%) had at least 1 clinical outcome. One patient had recurrent bouts of pulmonary edema; they were thought to be ischemic in origin and associated with a gradual decrease in left ventricular ejection fraction (assessed by 2-dimensional echocardiogram) before death. Four other patients experienced episodes of pulmonary edema thought to be due to recurrent ischemia, and 11 patients had subsequent postinfarction angina. In contrast, among the 32 patients in group 2, only 7 had at least 1 ischemic event (22%). One patient had pulmonary edema, 1 died of cardiac rupture and 6 patients experienced subsequent angina after infarction. The difference in incidence of combined outcomes between the 2 groups (52 vs 22%) is significant (p <0.02). There was a greater frequency of pulmonary edema (p = 0.06) and postinfarction angina

TABLE IV Clinical Ischemic Events During Hospital Stay

	ST Changes (n = 27)	No ST Changes (n = 32)	p Value
Death (%)	1 (4)	1 (3)	NS
Recurrent MI (%)	0 (0)	0 (0)	NS
Pulmonary edema (%)	5 (19)	1 (3)	0.06
Angina after AMI (%)	11 (41)	6 (19)	0.06
At least 1 ischemic outcome (%)	14 (52)	7 (22)	<0.02

(p = 0.06) of borderline statistical significance in the patients with silent ischemia compared to those without silent ischemia. All of the patients who experienced new onset pulmonary edema during the later in-hospital stay had ejection fractions of >45% on 2-dimensional echocardiogram performed within the first few days after AMI. In this study the total duration of ischemia did not further separate patients into high- and low-risk groups. Of the 13 patients with <60 minutes of silent ischemia, 6 had ischemic outcomes compared to 8 of 14 with >60 minutes of ischemia.

#### DISCUSSION

AMI is associated with significant prehospital, inhospital and 1-year mortality and morbidity. Many studies have shown that the factors that predict outcome after AMI include the amount of myocardial damage, 2,5,19 the severity of ventricular dysrhythmias and the presence of recurrent or inducible ischemia. 3,4,20 The latter can often be identified by predischarge exercise treadmill testing. 3,4 However, a proportion of patients develop evidence of recurrent ischemia early after AMI, and others are unable to exercise for a variety of reasons that may include peripheral vascular disease, musculoskeletal problems or general frailty. The early identification of patients likely to experience recurrent in-hospital ischemia might guide earlier institution of medical therapy or investigation.

Transient myocardial ischemia on ambulatory electrocardiographic monitoring is frequently asymptomatic in patients with stable exertional angina and unstable angina, and in patients 2 weeks after infarction.<sup>3,9,12,15-17</sup> Although the baseline electrocardiogram may be quite abnormal during the first 24 to 48 hours after AMI, the ST segments have often returned to baseline by 2 days after admission and further transient ST-segment changes can be interpreted on ambulatory electrocardiographic monitoring in most patients.

We have shown that in patients considered at high risk after AMI because of high grade ventricular arrhythmias and low ejection fraction, ischemia on predischarge monitoring identified patients with increased mortality after hospital discharge.<sup>17</sup> Others have found ambulatory electrocardiographic monitoring to have similar prognostic importance in more stable patients investigated later after AMI.<sup>18</sup> In this study, stable patients were monitored in the first 3 to 5 days after AMI to determine the frequency of ischemic electrocar-

diographic changes occurring in the very early postinfarction period, and to determine whether its presence was correlated with subsequent overt ischemic events during the hospital stay. Forty-six percent of the patients studied had asymptomatic ischemic episodes on 48 hours of continuous electrocardiographic monitoring early after infarction. This rather high incidence of ischemia may be due in part to very early monitoring, which identified patients who developed subsequent symptomatic ischemia requiring early intervention. These patients would not be available for later predischarge study. These patients were not clinically different from those who showed no ischemia with regard to risk factors, type of AMI, degree of creatine phosphokinase rise, antianginal medications at the time of monitoring, prior thrombolysis or extent of coronary artery disease. A high percentage of the patients studied had early asymptomatic ischemic episodes despite the use of antianginal medication. The practice at our institution is to use antiischemic medications prophylactically in patients after AMI. Despite this, the group of patients who demonstrated ischemic episodes on continuous electrocardiographic monitoring had a significantly higher incidence of overt clinical ischemic episodes during their hospital stay. The increased incidence of pulmonary edema in the patients with silent ischemia despite normal overall ejection fractions suggests that repetitive episodes of ischemia may lead to transient left ventricular dysfunction.

At the present time, insufficient data are available to indicate whether ambulatory electrocardiographic monitoring provides prognostic information beyond that obtained using the standard risk-stratification variables, including exercise treadmill testing in the broad spectrum of postinfarction patients. This has been found in studies of stable angina,21 where ambulatory electrocardiographic monitoring provided added prognostic information above and beyond exercise test results. Similar results have been reported for patients with unstable angina<sup>15</sup> and for patients considered at high risk after AMI<sup>17</sup> who may not be suitable candidates for exercise treadmill testing.

Thus, although a limited amount of data examining the independent value of ambulatory electrocardiographic monitoring and exercise treadmill testing exist, at the present time it seems prudent to consider ambulatory electrocardiographic monitoring as an alternative method to detect transient, usually asymptomatic myocardial ischemia, when exercise treadmill testing is not appropriate. The in-hospital period very early after AMI may be a time when this information would be clinically useful. However, this would depend on the rapid availability of this information to the clinician. The recent availability of real-time ST-segment analysis could allow immediate access to data on ST trends and ischemic episodes.<sup>22,23</sup> This would appear well suited for needs requiring rapid data analysis.

Acknowledgment: We wish to thank Valerie Williams and Kimberly Bobo for secretarial assistance.

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CLINICAL PHARMACOLOGY, INDERAL is a nonselective, beta-adrenergic receptor-

CLINICAL PHARMACOLOGY. INDERAL is a nonselective, beta-adrenergic receptor-blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor-stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vaso-dilator responses to beta-adrenergic stimulation are decreased proportionately. INDERAL LA Capsules (60, 80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL Tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg-for-mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL La from conventional propranolol, a possible need for retirration upwards should be considered especially to mainproparation, a possible head for fettifation upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure, and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the manage ment of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerphated by beta-recentor stimulation. the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation Clinical improvement may be temporary.

INDERAL LA

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first-degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE: Sympa warnings. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (eg, chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors. MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

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INDERAL (propranolol HCI), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, eg. dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers. DIABETES AND HYPOGLYCEMIA: Beta blockers should be used with caution in diabets. Date to be the blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. Following insulin-induced hypoglycemia, propranolol may cause a delay in the recovery of blood cilucose to normal levels.

significantly affected. Following insulin-induced hypoglycemia, propranolol may cause a delay in the recovery of blood glucose to normal levels.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid function tests, increasing T<sub>4</sub> and reverse T<sub>4</sub>, and decreasing T<sub>5</sub>.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case, this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. GENERAL: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL (propranolol HCI) is not indicated for the treatment of paired hepatic or renal func hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

CLINICAL LABORATORY TESTS. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase. DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL (propranolol HCI) is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, verligo, syncopal attacks, or orthostatic hypotension.

Caution should be exercised when patients receiving a beta blocker are administered a calcium-channel-blocking drug, especially intravenous verapamil, for both agents may depress myocardial contractility or attrioventricular conduction. On rare occasions, the concomitant intravenous use of a beta blocker and verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction.

Aluminum hydroxide gel greatly reduces intestinal absorption of propranolol.

Ethanol slows the rate of absorption of propranolol.

Phenytoin, phenobarbitone, and rifampin accelerate propranolol clearance.

Chlorpromazine, when used concomitantly with propranolol, results in increased plasma

levels of both drugs.

Antipyrine and lidocaine have reduced clearance when used concomitantly with propranolol.

Thyroxine may result in a lower than expected T<sub>3</sub> concentration when used concomitantly

with propranolol

Cimetidine decreases the hepatic metabolism of propranolol, delaying elimination and increasing blood levels.

increasing blood levels.

Theophylline clearance is reduced when used concomitantly with propranolol.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

PREGNANCY: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. NURSING MOTHERS: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

nen INDERAL is administered to a nursing woman.
PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely

required the withdrawal of therapy.

Cardiovascular: Bradycardia: congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the

Raynaud type.

Central Nervous System: Light-headedness; mental depression manifested by insomnia, Central Nervous System: Light-headedness; mental depression progressing to catalonia; visual

Central Nervous System: Light-headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatoria; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate formulations, fatigue, lethargy, and viderams appear dose related.

Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea,

tric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic: Pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respira-

60 mg 80 mg 120 mg 160 mg

Respiratory: Bronchospasm.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been excepted with programmed. been associated with propranolol

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL Tablets to INDERAL LA Capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg-for-mg substitute for INDERAL INDERAL LA has different kinetics and produces lower blood levels. Retiration may be necessary, especially to maintain effectiveness at the end of the 24-hour dosing interval. HYPERTENSION — Dosage must be individualized. The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily, or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily, In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—Dosage must be individualized. Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three- to seven-day intervals until optimal response is obtained. Although individual patients may respond at any dosage level, the everage optimal dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

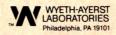
If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

WARNINGS).

MIGRAINE — Dosage must be individualized. The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimal migraine prophylaxis. If a satisfactory response is no totalined within four to six weeks after reaching the maximal dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several

weeks.
HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.
PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

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# Effects of Cigarette Smoking and Propranolol in Survivors of Acute Myocardial Infarction

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The effect of propranolol on mortality and reinfarction after acute myocardial infarction (AMI) in cigarette smokers and nonsmokers was studied in the Beta Blocker Heart Attack Trial. Cigarette smokers (n = 2,332) were 5 years younger than nonsmokers and had a lower incidence of diabetes mellitus, systemic hypertension, previous AMI and cardiomegaly. Among cigarette smokers, the placebo group had a higher total mortality rate than the propranolol group (11.0 vs 7.4%, p <0.0008) and more sudden cardiac deaths (7.1 vs 4.6%, p <0.009). In nonsmokers the placebo group had a mortality (7.9 vs 7.1%, p >0.64) similar to the propranolol group. After baseline adjustment, cigarette smokers were estimated to have 1.6 times the risk of dying as compared to nonsmokers (p <0.0007). Adjusting for baseline differences, both treatment with propranolol and nonsmoking were predictors of survival. No detectable nonsmoking/ propranolol interaction could be identified. In survivors of AMI a beneficial effect of propranolol is observed for cigarette smokers. Nevertheless, cigarette smoking continues to be a risk factor for mortality after AMI even for those receiving propranolol.

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ong-term therapy with the  $\beta$ -adrenergic blocking agents has been shown to reduce mortality in patients who have had an acute myocardial infarction (AMI).1-3 Examination of the Norwegian Multicenter Study indicated that timolol yielded a greater benefit in reducing mortality in cigarette smokers than in nonsmokers.4 The efficacy of propranolol in relation to smoking habits of AMI patients has not been previously reported. Cigarette smoking has been shown to increase heart rate and blood pressure and alter platelet function.<sup>5,6</sup> Propranolol, due to its effects on heart rate, blood pressure and platelet function, has the potential of attenuating the adverse consequences of smoking. 7.8 In this retrospective analysis of the Beta Blocker Heart Attack Trial (BHAT), we examined propranolol's efficacy on mortality and reinfarction as it relates to the cigarette smoking habits of patients with AMI. In addition, we examined the independent impact of smoking behavior on cardiac events after AMI, after taking the beneficial effects of propranolol into account.

#### **METHODS**

Patients studied were participants in the BHAT, a randomized multicenter, double-blind, placebo-controlled trial, designed to test whether propranolol reduces mortality in survivors of AMI. Within 5 to 21 days after hospital admission, 3,837 patients were randomized. The average follow-up was 25.1 months.

The outcomes studied include total mortality, coronary artery disease mortality, sudden coronary mortality and reinfarction. All patients were questioned about their smoking habits (Appendix 2) at entry to the trial and at each follow-up visit. Smokers are defined as those patients who reported smoking cigarettes at entry to the study or who quit smoking <1 year before their AMI (n = 2,332). Nonsmokers were defined as those who had never smoked or quit smoking >1 year before their AMI (n = 1,186). Continuing smokers included smokers who continued to smoke (n = 627) after the AMI. Patients who smoked only pipes or cigars (n = 319) were excluded.

The baseline variables of smokers and nonsmokers were compared using t tests for continuous variables and chi-square tests for categorical variables. These baseline variables were used in other analyses of morbidity and mortality in the BHAT population. Survival curves for propranolol and placebo within the smoking groups used log rank tests. Cox proportional hazards regression analysis was used to test for smoking, treatment and a smoking-treatment interaction after adjusting for the baseline variables (Table I). Proportional

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\*See Appendix 1.

Baseline Variable	Smokers* (n = 2,332)	Nonsmokers <sup>†</sup> $(n = 1,186)$	p Value
Propranolol (%)	50	50	>0.92
Male sex (%)	84	82	>0.11
White (%)	88	91	< 0.005
Mean age (yrs)	53 ± 8.5	$59 \pm 7.4$	< 0.001
Mean heart rate (beats/min)	$76 \pm 9.8$	77 ± 9.7	< 0.001
Mean hematocrit (%)	$41 \pm 6.5$	41 ± 6.6	>0.12
Mean CPK ratio	$11 \pm 9.7$	9 ± 7.8	< 0.001
Medical history (%)‡			
Prior AMI	14	16	< 0.04
Hypertension	37	49	< 0.001
Angina	37	37	>0.92
Congestive heart failure	9	10	>0.11
Diabetes	9	16	< 0.001
Receiving propranolol or other β- blocker before AMI (%)	7	8	>0.16
In-hospital events before randomization (%)			
Atrial fibrillation	6	8	< 0.02
Ventricular tachycardia	24	22	>0.10
Use of antiarrhythmic drug	47	45	>0.26
Medications at randomization (%)			
Antiarrhythmic	17	18	>0.39
Anticoagulant	14	15	>0.45
Antiplatelet	7	7	>0.68
Diuretic	15	21	< 0.001
Digitalis	11	15	< 0.002
Oral hypoglycemic	1	3	< 0.001
ECG abnormalities (%)			
Q-QS waves	65	71	< 0.002
ST depression	25	29	< 0.02

Ventricular conduction defects

Cardiomegaly (%)§

Holter findings (%) >10 VPCs

Complex VPCs1

Location of AMI (%)

Subendocardial

Non-BHAT AMI

Anterior and inferior

Anterior

Inferior

TABLE I Baseline Comparison of Cigarette Smokers and Nonsmokers

Nonsmokers and those patients who never smoked or quit smoking >1 year before AMI.

Nonsmokers and those patients who never smoked or quit smoking >1 year before AMI.

Cardiomegaly = cardiothoracic ratio >50%; 340 smokers and 199 nonsmokers had missing information.

Complex VPCs = >10 VPCs/hr, multiform VPCs, couplets, or ventricular tachycardia.

CPK ratio = ratio of highest CPK level to the expected upper limit for the laboratory.

AMI = acute myocardial infarction; BHAT = Beta Blocker Heart Attack Trial; CPK = creatine phosphokinase; ECG = electrocardiogram; VPC = ventricular premature complex. All ± data are mean ± standard deviation.

9

33

10

33

27

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32

25

hazards assumptions were also tested but were not used in all analyses.

#### RESULTS

Baseline comparisons: Approximately equal proportions of cigarette smokers and nonsmokers received propranolol. At entry to the trial 78% of the smokers smoked >1 pack of cigarettes/day. The median duration of smoking was 34 years (range 1 to 63). Nonsmokers had a greater prevalence of most risk factors associated with death after an AMI (Table I). Nonsmokers were about 5 years older and had an increased incidence of prior AMI, hypertension, diabetes mellitus, atrial fibrillation, cardiomegaly and use of digitalis and diuretics. In addition, nonsmokers had an increased frequency of Q-QS waves, ST depression on the electrocardiograms and an increased frequency of ventricular premature beats during 24-hour ambulatory electrocardiographic recordings. Smokers had a higher frequency of subendocardial AMI, which probably explains the observed difference in the location of AMI in the 2 groups. Despite these differences favoring an increased mortality rate in the nonsmoking group, the observed placebo mortality rate for cigarette smokers was significantly greater than that for nonsmokers (11.0 vs 7.9%, p <0.04 log rank test).

>0.86

< 0.001

< 0.02

>0.08

< 0.002

9

41

13

36

26

11

34

19

Efficacy of propranolol in relation to smoking habits: In the cigarette smokers, the placebo group had a higher total mortality than the propranolol group (11.0 vs 7.4%, p <0.0008, log rank test) (Figure 1 and Table II). There were also fewer coronary artery disease deaths and sudden coronary deaths in the propranolol-

Cigarette smokers and those patients who quit smoking in the year before AMI.

treated group. In nonsmokers, no detectable difference in any cardiac event was observed between the propranolol and placebo groups (Figure 2 and Table II).

After adjusting for baseline variables using Cox analyses, both propranolol and cigarette smoking remained predictors of mortality (p <0.002 and p <0.0007) without any interaction (p >0.19). Smokers were estimated to be 1.6 times as likely to die as non-smokers (95% confidence interval 1.2, 2.1), despite the beneficial effects of propranolol, using Cox regression analysis. A 47% decrease in total mortality was observed for the subset of continuing smokers, a decrease of 32% in all smokers and 10% in nonsmokers (Table II, Figure 3).

#### DISCUSSION

This is the first report to explore the effect of propranolol on mortality and reinfarction in cigarette smokers in patients after AMI. Our study supports previous observations that cigarette smoking has an adverse effect on mortality after an AMI.9,10 This study confirms that cigarette smokers have a higher mortality despite lower risk factors favoring survival.3,11,12 It also indicates that propranolol has a salutary effect on those who smoke. The subset of propranolol-treated individuals who were cigarette smokers before the AMI and continued to smoke had a lower total mortality, coronary artery disease mortality and sudden death rate compared to the placebo group. In fact, the group of propranolol-treated smokers as a whole had a mortality rate similar to the placebo nonsmoker group. In the smoking group, propranolol appears to exhibit its most

TABLE II Comparison of Outcomes by Treatment Group for Cigarette Smokers, Nonsmokers and Continuing Smokers in the RHAT

	Propranolol % with Outcome	Placebo % with Outcome	Log Rank Test p Value
Smokers*	(n = 1,166)	(n = 1,166)	
Mortality	7.4	11.0	<0.0008
CAD mortality	6.5	9.9	<0.003
Sudden CAD death	4.6	7.1	<0.009
Reinfarction	4.5	4.6	>0.71
Nonsmokers†	(n = 591)	(n = 595)	
Mortality	7.1	7.9	>0.64
CAD mortality	6.6	7.2	>0.69
Sudden CAD death	5.1	5.4	>0.83
Reinfarction	4.4	5.9	>0.27
Continuing smokers‡	(n = 321)	(n = 308)	
Event			
Death	11.5	21.8	< 0.0005
CAD mortality	10.6	19.8	< 0.0009
Sudden CAD death	8.4	14.6	<0.01
Reinfarction	4.7	4.9	>0.72

<sup>\*</sup> Current cigarette smokers and those patients who quit smoking in the year before AMI.

profound effect on total and sudden death rather than reinfarction in the smoking group. Although the effect of propranolol on mortality after AMI was observed only in smokers, there was no statistically significant propranolol interaction with smoking status.

These results represent a post hoc analysis of a clinical trial designed to test the efficacy of propranolol in

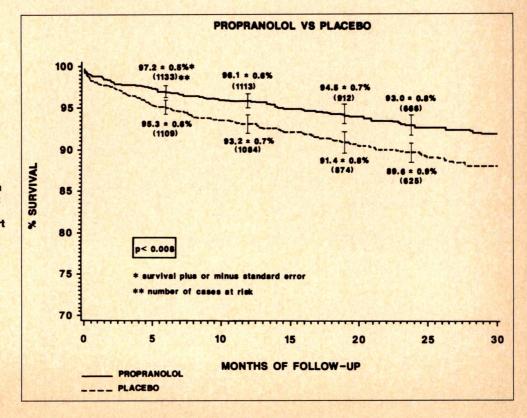


FIGURE 1. Survival in smokers by treatment groups for patients in the Beta Blocker Heart Attack Trial.

before AMI.

† Nonsmokers and those patients who never smoked or quit smoking >1 year before AMI.

AMI = acute myocardial infarction; CAD = coronary artery disease.

patients after AMI and are consistent with a similar analysis in the Norwegian trial.<sup>12</sup> In that study, treatment with timolol decreased total mortality and sudden death. Frequency of nonfatal reinfarction was similar in smokers receiving timolol and placebo, and lower in

timolol-treated nonsmokers. However, in the Medical Research Council trial, a statistically significant protective effect of propranolol was detected for fatal and nonfatal coronary events only in nonsmokers. <sup>13</sup> This cohort, however, was a group of hypertensive patients. In addi-

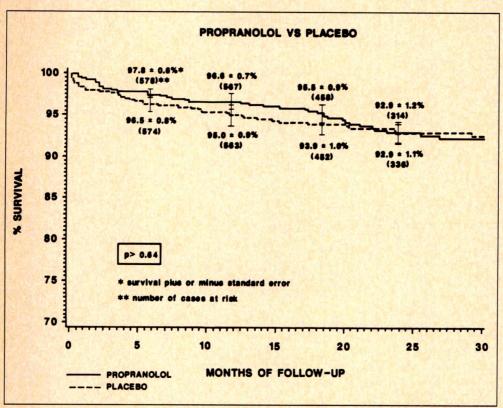


FIGURE 2. Survival in nonsmokers by treatment groups for patients in the Beta Blocker Heart Attack Trial.

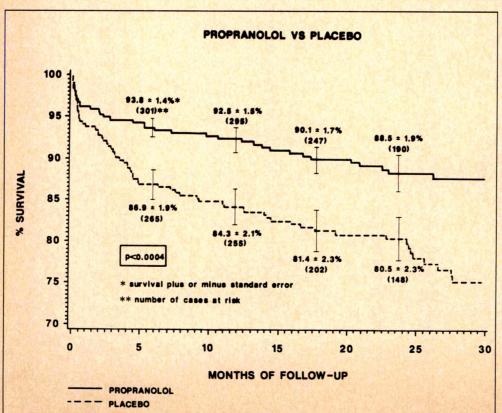


FIGURE 3. Survival in continuing smokers by treatment groups for patients in the Beta Blocker Heart Attack Trial.

tion, the trial had limited power to detect differences in subset analyses, a problem experienced in this analysis

of propranolol-smoking interactions.

The specific mechanism by which  $\beta$  blockers produce a beneficial effect on smokers after AMI is uncertain. Beta blockers can decrease pulse rate and blood pressure and can affect platelet function.8 Nicotine increases heart rate and systolic blood pressure, which increases myocardial oxygen demands<sup>5</sup> that can be prevented by adrenergic blockade with phentolamine and propranolol.7 Nicotine also decreases myocardial oxygen supply because of increased blood carbon monoxide content<sup>14</sup> as well as by coronary vasoconstriction. 15 Smoking influences the hemostatic system by its effects on platelets and indirectly by endothelial damage.16 Propranolol, in contrast, decreases platelet aggregation<sup>8,17</sup> and circulating platelet aggregates, <sup>18</sup> inhibits platelet adhesion and also interferes with clot retraction.19

The benefits of propranolol therapy in patients who continued to smoke after an AMI are shown dramatically by comparing mortality rates for those who continue to smoke (11.5%) to both smokers and nonsmokers before AMI (7.4%). In conclusion, this analysis of the BHAT demonstrates a beneficial effect of propranolol on mortality in cigarette smokers who survived an AMI and those who continued to smoke after their AMI. Despite the beneficial effect of propranolol in cigarette smokers surviving an AMI, smoking remained a predictor of mortality in both propranolol- and placebotreated patients.

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#### **APPENDIX 1**

Beta Blocker Heart Attack Trial Principal Investigators and Staffs:

Clinical Centers: Baylor College of Medicine, Houston, Texas: Craig M. Pratt, MD; Boston University School of Medicine, Boston, Massachusetts: Pantel S. Vokonas, MD; Brown University Affiliated Hospitals, Providence, Rhode Island: Robert J. Capone, MD; Emory University, Atlanta, Georgia: Robert C. Schlant, MD; Evanston Hospital, Evanston, Illinois: Gary N. Wilner, MD; Geisinger Medical Center, Danville, Pennsylvania: Charles A. Laubach, MD; Greater Baltimore Medical Center, Baltimore, Maryland: Thaddeus E. Prout, MD; Henry Ford Hospital, Detroit, Michigan: Gerald M. Breneman, MD; Kaiser Foundation Hospital, Portland, Oregon: John A. Grover, MD; Lankenau Hospital, Philadelphia, Pennsylvania: William L. Holmes, PhD; Long Island Jewish-Hillside Medical Center, New Hyde Park, New York: Kul D. Chadda, MD; Maimonides Medical Center, Brooklyn, New York: Edgar Lichstein, MD; Medical College of South Carolina, Charleston, South Carolina: Peter C. Gazes, MD; Medical College of Virginia, Richmond, Virginia: David W. Richardson, MD; Miami Heart Institute, Miami, Florida: Frank L. Canosa, MD; Montreal Heart Institute, Montreal, Quebec, Canada: Pierre A. Theroux, MD; Mt. Sinai Hospital, Minneapolis, Minnesota: Philip J. Ranheim, MD; Northwestern University Medical School, Chicago, Illinois: Olga M. Haring, MD; Overlook Hospital, Summit, New Jersey: John J. Gregory, MD; Pacific Health Research Institute, Honolulu, Hawaii: J. Judson McNamara, MD; Providence Medical Center, Portland, Oregon: Gordon L. Maurice, MD; Rush Presbyterian-St. Luke's Medical Center, Chicago, Illinois: James A. Schoenberger, MD; Rutgers Medical School-Raritan Valley Hospital, New Brunswick, New Jersey: Peter T. Kuo, MD; Salt Lake Clinical Research Foundation, Salt Lake City, Utah/Ogden Reseach Center, Ogden, Utah: Allan H. Barker, MD, C. Basil Williams, MD; State University of New York at Buffalo, Buffalo: Robert M. Kohn, MD; University of California at Davis, Davis: Nemat O. Borhani, MD; University of California, San Francisco: May Anne Warnowicz, MD; University of Rochester School of Medicine, Rochester: Paul N. Yu, MD; University of Southern California at Los Angeles, Los Angeles: L. Julian Haywood, MD; Veterans Administration Hospital, Little Rock, Arkansas: Marvin L. Murphy, MD; Veterans Administration Hospital, West Roxbury, Massachusetts: Kevin M. McIntyre, MD.

Coordinating center: University of Texas, Houston: C. Morton Hawkins, ScD, Director.

Central laboratory: Bio-Science Laboratories, Van Nuys, California: Frank Ibbott, PhD.

Resting electrocardiogram reading center: University of Minnesota, Minneapolis: Richard S. Crow, MD.

Ambulatory electrocardiogram reading center: Anthropometric Heart Clinic, Haddonfield, New Jersey: Joel Morganroth, MD.

Drug distribution center: Department of Health and cigarettes did you smoke per day? Human Services, United States Public Health Service, Perry \_\_\_\_None -< $\frac{1}{2}$  pack Point, Maryland: Clifford Brennan.  $-1\frac{1}{2}$  to <2 packs \_\_\_\_ 2 or more packs National Heart, Lung, and Blood Institute: Bethesda: 4. Just before this hospitalization, did you still smoke William T. Friedewald, MD, Associate Director for Clinical cigarettes? Applications and Prevention. Yes (Skip to 6) \_No **APPENDIX 2** \_\_\_\_ <6 mos ago **Lifestyle Questionnaire** \_\_ 6 mos to 12 mos ago \_\_\_\_ 12 mos to 5 yrs ago 1. Have you ever smoked cigarettes? \_ 5 or more yrs ago \_\_\_\_Yes \_\_\_\_ No (Skip to 6)

2. Approximately how many years have you smoked cigarettes? Years If <1 year, code 01

3. During those years, on an average, how many

# Role of Previous Angina Pectoris and Collateral Flow to Preserve Left Ventricular Function in the Presence or Absence of Myocardial Infarction in Isolated Total Occlusion of the Left Anterior Descending Coronary Artery

Yves Juillière, MD, Nicolas Danchin, MD, Alain Grentzinger, MD, Christine Suty-Selton, MD, Jean P. Lethor, MD, Thierry Courtalon, MD, Claude Pernot, MD, and François Cherrier, MD

The aim of this study was to determine whether previous angina pectoris and collateral circulation influenced myocardial function after isolated coronary occlusion. In 58 consecutive patients, coronary angiography showed a complete isolated occlusion of the left anterior descending coronary artery; 43 patients (74%) had previous myocardial infarction. Duration of previous angina pectoris was defined as the time from the first ischemic symptom to the date of myocardial infarction or of coronary angiography in the absence of myocardial infarction. Left ventricular ejection fraction was measured on the 30° right anterior oblique projection of the left ventricular angiogram. Collateral circulation was graded as follows: none or filling limited to side branches (group 1) and partial or complete filling of the epicardial arterial segment (group 2). Group 2 (40 patients) had higher ejection fraction (57 vs 38%; p <0.0001) and longer duration of previous angina pectoris (11 vs 0.1 months; p <0.002) than group 1 (18 patients). A longer duration of previous angina pectoris probably allows collateral development before coronary occlusion in 1-vessel coronary artery disease, thereby limiting myocardial damage.

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The role of coronary collateral circulation in protecting myocardium after the occlusion of a supplying artery has long been debated.1-6 Recent data show that the extent of myocardial alteration after coronary occlusion depends on the existence of collateral circulation.<sup>7-9</sup> It has also been shown that spontaneous obstruction of high degree coronary artery stenoses is frequently well tolerated with little myocardial damage, 8,10,11 presumably due to the development of collateral circulation. Although some conflicting studies have previously attempted to show the relation between the extent of development of collateral channels and the existence of angina pectoris before infarction,7,12-14 the role of the duration of previous angina pectoris on the development of collateral circulation has not been documented yet. The present study assesses the protective role of the duration of previous angina pectoris on the preservation of myocardial function after isolated occlusion of the left anterior descending (LAD) coronary artery in patients with 1-vessel coronary artery disease and relates this effect to the presence of well-developed collateral circulation.

#### **METHODS**

Study population: From January 1985 to December 1987, 58 consecutive patients who underwent their initial coronary angiography at our institution were found to have a complete isolated occlusion of the LAD. No patient had valvular heart disease, congenital heart disease, myocardial disease or previous cardiac surgery. No patient had ≥50% stenosis in any of the other coronary vessels.

Coronary angiography was justified in all patients by the existence of clinical ischemic symptoms, angina pectoris or myocardial infarction. The diagnosis of myocardial infarction was based on the presence of at least 2 of the following criteria: compatible clinical history, characteristic electrocardiographic changes or an increase in appropriate serum enzyme levels. Angina pectoris was considered to be present before myocardial infarction only if it occurred >7 days before the onset of acute myocardial infarction.

Duration of previous angina pectoris was defined as the time from the first symptom to the date of myocar-

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TABLE I Comparison of Mean Values of LVEF and Duration of Preceding AP\* According to the Different Grades of Collateralization

	LVEF (%)	p Value	AP (mos)	p Value
Group 1				A Stone
Grade 0 (5 pts)	33 ± 13		0±0	
		NS		NS
Grade 1 (13 pts)	$39 \pm 10$		$0.2 \pm 0.4$	
Group 2				
Grade 2 (13 pts)	$56 \pm 17$		$17 \pm 33$	
		NS		NS
Grade 3 (27 pts)	$60 \pm 12$		8 ± 20	

TABLE II Comparison of Mean Values of LVEF and Duration of Preceding AP in the Group with Poorly Developed Collaterals (Group 1) and in the Group with Well-Developed Collaterals (Group 2)

	LVEF (%)	AP (mos)
Group 1 (18 pts)	38 ± 11 *	0.1 ± 0.3
Group 2 (40 pts)	57 ± 15	11 ± 25

Data are mean ± standard deviation \*p <0.0001, Student unpaired t test for LVEF; †p <0.002, Mann and Whitney's opparametric test for AP.

Abbreviations as in Table I.

dial infarction or of coronary angiography in the absence of myocardial infarction.

Cardiac catheterization: Left ventriculography was routinely performed in the 30° right anterior oblique projection and calculation of left ventricular ejection fraction was based on the area-length method. 15

All patients underwent selective coronary angiography using the femoral approach and 7Fr catheters, performed by manual injections of 4 cc of Renografin® in multiple projections (at least 5 different projections for the left coronary artery and 3 for the right coronary artery). Collateral vessels were scored by 2 independent observers according to the degree of opacification of the

native vessel distal to its occlusion. Collateral vessels were assigned a numeric score between 0 and 3 according to the criteria of Cohen and Rentrop. 16 The classification system is summarized as follows: grade 0 = no visible filling of any collateral channels; grade 1 = filling of side branches of the artery to be perfused via collateral vessels without visualization of the epicardial segment; grade 2 = partial filling of the epicardial segment by collaterals; and grade 3 = complete filling of the epicardial segment by collaterals.

When the degree of opacification varied in a given patient, the score corresponding to the best visualization of the distal vessel was used. In patients in whom the distal segment of the occluded vessel filled from both right and left coronary collateral vessels, the sum of the scores (not to exceed 3) was used.

This scoring system did not grade the collateral conduit itself, but rather the angiographic result of its presence as demonstrated by distal filling of a completely occluded artery. Furthermore, time required for opacification through collateral channels was not considered.

For the purpose of this study, the patients were classified in 2 groups according to these collateral criteria: group 1 designated patients with either grade 0 or 1 collaterals who were considered to have "poorly developed" collaterals; group 2 designated patients with either grade 2 or 3 collaterals who were considered to have "well-developed" collaterals.

Data analysis: All values are presented as mean ± standard deviation. Statistical analyses between each group used the Student unpaired t test for comparing the values of left ventricular ejection fraction and Mann and Whitney's nonparametric test for comparing the values of duration of previous angina pectoris. A p value <0.05 was considered to be significant.

#### RESULTS

The mean age of the population was  $53 \pm 10$  years (range 30 to 76); 45 were men and 13 were women. Among these 58 patients, 23 had an occlusion of the proximal LAD, 29 an occlusion of the mid-LAD and 6

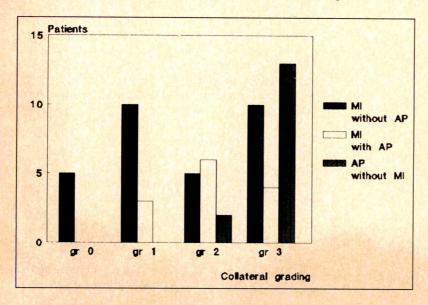


FIGURE 1. Comparison of patients according to the ischemic symptoms and the collateral grading. AP = previous angina pectoris; MI = myocardial infarction.

Data are mean ± standard deviation.

\* Student unpaired t test was used for LVEF and Mann and Whitney's nonparametric test for AP.

AP = angina pectoris; LVEF = left ventricular ejection fraction; NS = not significant.

an occlusion of the distal LAD coronary artery. The degree of collateral circulation was as follows: 5 patients in grade 0, 13 in grade 1, 13 in grade 2 and 27 in grade

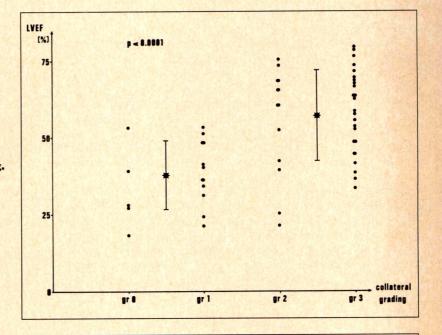
When the patients were compared according to the clinical ischemic symptoms and the degree of collateral circulation (Figure 1), it was shown that all patients in grade 0 had had a myocardial infarction without previous angina pectoris. Furthermore, patients in grade 0 and 1 were patients with myocardial infarction; none of them had angina pectoris without myocardial infarction. Patients in grade 3 included the highest percentage with angina pectoris, particularly without myocardial

With regard to left ventricular ejection fraction and duration of angina pectoris, there was no significant difference in group 1 patients between those with grade 0 or 1 collaterals and, in group 2 patients, between those with grade 2 or 3 collaterals (Table I).

Table II lists the mean values of ejection fraction and duration of angina pectoris for the 2 groups. Left ventricular ejection fraction was significantly higher (p <0.0001) in the group with well-developed collaterals (Figure 2). In addition, the duration of angina pectoris was significantly longer (p <0.002) in this group (Figure 3).

When we compared ejection fraction and duration of angina pectoris, the group of 30 patients without previous angina pectoris had a lower left ventricular ejection fraction than the group of 28 patients with previous angina pectoris (44  $\pm$  16 vs 58  $\pm$  14%, p <0.001) (Figure

FIGURE 2. Comparison of individual values of left ventricular ejection fraction (LVEF) according to the collateral grading. The mean values (\*) associate patients in grades 0 and 1 (group 1) and patients in grades 2 and 3 (group 2).



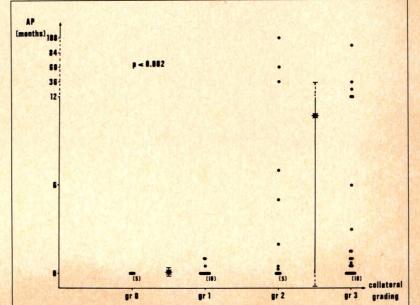


FIGURE 3. Comparison of individual values of duration of previous angina pectoris (AP) according to the collateral grading. The mean values (\*) associate patients in grades 0 and 1 (group 1) and patients in grades 2 and 3 (group 2).

TABLE III Comparison of Mean Values of LVEF and Duration of Preceding AP in the Group with Poorly Developed Collaterals (Group 1) and in the Group with Well-Developed Collaterals (Group 2) After Eliminating the Patients with an Interval Between Myocardial Infarction and Cardiac Catheterization > 1 Month

the second secon	the state of the s	
	LVEF (%)	AP (mos)
Group 1 (13 pts)	39 ± 10	0.1 ± 0.3
Group 2 (28 pts)	58 ± 13	13 ± 27

Data are mean ± standard deviation bata are mean  $\pm$  standard deviation. \*p < 0.0001, Student unpaired t test for LVEF; †p < 0.0004, Mann and Whitney's onparametric test for AP.

Abbreviations as in Table I.

The time period from myocardial infarction to coronary angiography was not statistically different between group 1 and 2 (1.5  $\pm$  1.5 vs 9  $\pm$  20 months). However, some group 2 patients had been catheterized several months after their myocardial infarction; in such patients, left ventricular ejection fraction could have been improved by compensatory hypertrophy of noninfarcted myocardium. Table III lists similar results after eliminating the patients with an interval between myocardial infarction and cardiac catheterization >1 month.

When only myocardial infarction was considered, left ventricular ejection fraction was always lower in group 1 (38  $\pm$  11%) than in group 2 (53  $\pm$  16%) (p <0.02) but duration of previous angina pectoris was not significantly different (0.1  $\pm$  0.3 in group 1 vs 4  $\pm$  14 months in group 2). However, only 3 patients of the 18 patients in group 1 versus 10 of the 25 patients in group 2 had previous angina pectoris, suggesting a possible influence of angina pectoris on development of collateral circulation (Figure 1).

### DISCUSSION

Angiographic assessment of the degree of collateral development is easy16 and correlates with the functional capacity of these collateral vessels. 17,18 Elayda et al5 showed that collateral circulation could not be seen angiographically unless there was total or near-total occlusion. In our study, all LAD arteries were totally occluded and no competition of anterograde flow interfered. Furthermore, lateral myocardial dysfunction cannot be appreciated by left ventricular angiography in the right anterior oblique projection and we thus considered only occlusions of the LAD. Lastly, we excluded patients with stenoses of the other coronary arteries that could have caused angina pectoris or impeded the development of collaterals to the LAD.

It is now well established that the degree of altered left ventricular function after coronary occlusion depends on the presence or absence of collaterals.8,14,19,20 Spontaneous occlusion of severe coronary stenoses is frequently well tolerated, with little alteration of myocardial function and, often, disappearance of clinical ischemic symptoms.<sup>10</sup> This evolution is likely to be related to the development of collateral circulation, an inverse quantitative relation existing between stenosis severity and collateral function.8,11

Angina pectoris is the clinical correlate of myocardial ischemia. However, when presence or absence of angina before the occlusive event has been studied, 9,12,13,20 the duration of previous angina pectoris was never considered. We thus decided to consider the duration of previous angina pectoris and its existence if it appeared >7 days before the date of myocardial infarction or of the date of coronary angiography.<sup>12</sup> Bearing witness to the existence of a severe coronary stenosis, duration of angina pectoris might parallel the time course of pro-

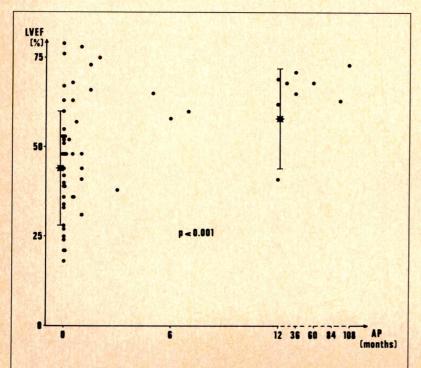


FIGURE 4. Comparison of individual values of left ventricular ejection fraction (LVEF) according to the duration of previous angina pectoris (AP). The mean values (\*) compare patients without AP to patients with AP.

gression of the disease and might represent the time that collateral circulation had to develop before coronary occlusion. Angina pectoris preceding the occlusive event was usually studied before myocardial infarction.<sup>7,13</sup> We preferred to use (as our inclusion criterion) total occlusion of the LAD assessed by coronary angiography rather than myocardial infarction (a possible consequence of coronary occlusion). Indeed, occlusions of the LAD without myocardial infarction correspond to the cases when collateral circulation is sufficiently developed to preserve myocardial function<sup>20</sup> and might develop during a longer phase of previous angina pectoris.

It had already been shown that the presence of collateral vessels to the occluded LAD is associated with preserved left ventricular function.20 Among patients with myocardial infarction and isolated total occlusion of the LAD, the symptom of angina pectoris before myocardial infarction could be a favorable sign in terms of preservation of left ventricular function.<sup>13</sup> Our study demonstrates that not only the presence, but also the duration, of angina pectoris plays an important role to allow a better development of collateral circulation, thereby improving left ventricular ejection fraction after coronary occlusion in 1-vessel coronary artery disease. However, some patients with well developed collaterals and good myocardial function had no previous angina pectoris or a duration of angina pectoris similar to that of patients with poorly developed collaterals. An ischemic stimulus promoting collateral development but unappreciated by the patients might have been present, suggesting a possible influence of silent ischemia in these individual cases.

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### **Left Atrial Function in Acute Transient Left Ventricular Ischemia Produced During Percutaneous Transluminal Coronary Angioplasty of the Left Anterior Descending Coronary Artery**

Ulrich Sigwart, MD, Milan Grbic, MD, Jean-Jacques Goy, MD, and Lukas Kappenberger, MD

Left atrial (LA) function was studied in 32 patients during percutaneous transluminal coronary angioplasty of the proximal left anterior descending artery with a dual micromanometer positioned transseptally in the left atrium and in the left ventricle. In 10 patients LA and left ventricular (LV) cineangiography was performed 30 minutes before percutaneous transluminal coronary angioplasty and 30 seconds after the occlusion of the left anterior descending coronary artery. Thirty seconds after left anterior descending occlusion, LV peak systolic pressure decreased from 135  $\pm$  12 to 106  $\pm$  9 mm Hg (p <0.05) and LV maximum dP/dt decreased from 1,634  $\pm$  136 to 1,137  $\pm$  127 mm Hg/s (p <0.01). Simultaneously, LA mean pressure increased from 11  $\pm$  2 to 29  $\pm$  1 mm Hg (p <0.001) and LA maximum dP/dt increased from 177  $\pm$  13 to 381  $\pm$  21 mm Hg (p <0.001). There was a difference between LV end-diastolic pressure and LA mean pressure of 1.5 mm Hg at rest and 7.8 mm Hg during ischemia and LA pulse pressure increased from 16  $\pm$  3 to 26  $\pm$  3 mm Hg (p <0.05) together with increase of LA A and V waves peak pressure. LV stroke volume index decreased from 46  $\pm$  5 to 43  $\pm$  3 ml/m<sup>2</sup> (difference not significant). The LA maximal volume increased from 18  $\pm$  2 to  $29 \pm 3 \text{ ml/m}^2$  (p <0.001). LA volume before LA contraction increased from 29  $\pm$  2 to 54  $\pm$  3 ml/m<sup>2</sup> (p <0.001). The LA stroke volume increased from 23  $\pm$  2 to 35  $\pm$  4 ml/m<sup>2</sup> (p <0.001) and the ratio of contribution of LA contraction to LV stroke volume index increased from 26  $\pm$  5 to 57  $\pm$  9% (p <0.001). LV isovolumic relaxation time shortened from 82  $\pm$  7 to 57  $\pm$  5 ms (p <0.001). Thus, left atrial function plays an important role in maintaining overall cardiac function during LV ischemia by reactive hyperactivity.

(Am J Cardiol 1990;65:282-286)

The left atrium is a muscular contractile chamber (located upstream of the left ventricle) that serves as a reservoir for storing blood during left ventricular (LV) contraction, as a conduit for blood from the pulmonary veins to the left ventricle during early ventricular filling and, most importantly, as a booster pump to complete LV filling. The role of atrial systole in maintaining optimal hemodynamic cardiac function has been studied extensively in animal models<sup>1-3</sup> and in humans.<sup>4-7</sup> A loss of atrial contraction as a result of atrial fibrillation8 or ventricular pacing9 reduces cardiac output by approximately 15 to 20%. The role of left atrial (LA) function has been demonstrated in experimental mitral regurgitation 10,11 and in patients after myocardial infarction. 12 Braunwald 15 has shown that the Frank-Starling mechanism may be operative in the left atrium as well as in the left ventricle. To assess the role of the left atrium in the presence of LV failure due to ischemia, we studied the LA function during acute myocardial ischemia induced by transient occlusion of the proximal left anterior descending coronary artery in 32 patients undergoing percutaneous transluminal coronary angioplasty.

### **METHODS**

Thirty-two patients, 28 men and 4 women, between 34 and 63 years old (mean  $52 \pm 7$ ) were studied. All patients were in normal sinus rhythm and none had a history of previous myocardial infarction. In each the indication for angioplasty was a significant proximal stenosis of the left anterior descending coronary artery. Informed consent was obtained from each patient and the study was approved by the ethical committee of the hospital. All patients were treated with aspirin, 1 g orally, the day before the study and diazepam, 5 mg orally, 1 hour before the procedure. A 7Fr double tipmanometer, the sensors separated by a distance of 5 cm, was placed transseptally via the femoral route. The distal sensor was located in the left ventricle and the proximal sensor in the left atrium. All pressures and their derivatives were recorded on photographic paper using a Honeywell LS 8 photographic recorder and simultaneously stored on digital tape. The recordings were made at a paper speed of 100 mm/s before and during transluminal coronary angioplasty. In 10 patients a 7Fr pigtail catheter was positioned in the pulmonary artery for contrast injections during angioplasty. We

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performed biplane left-sided coronary cineangiography at 50 frames/s during the injection of 45 ml of iopamidol 370 into the pulmonary artery. The cineangiography was obtained before angioplasty and after a waiting period of 20 minutes, and repeated at the end of a 30second left anterior descending balloon occlusion. The volume analysis of the LA and the LV chambers was performed according to standard methods. 13,14 Maximum LA volume (LA max [ml/m2]) was measured just before mitral valve opening. The minimum volume (LA volume min [ml/m<sup>2</sup>]) was measured at the end of atrial contraction, and the volume before LA contraction (LA volume pre A [ml/m<sup>2</sup>]) was taken just before LA A wave. LV volumes were measured during the same cycle. We calculated LV volume before LA contraction (LV volume pre A [ml/m<sup>2</sup>]), LV end-diastolic volume and LV end-systolic volume. The LA volume change (stroke volume) was calculated as LA volume max - LA volume min (ml/m<sup>2</sup>). LA contribution to LV filling was determined by subtracting the LA stroke volume from the LV stroke volume.

The on-line computer analyses of pressures and derivatives were compared with the analog tracings. The isovolumic relaxation time was determined as the interval from the aortic valve closure to the mitral valve opening. In 5 patients studied without a tipmanometer in the aortic root, the aortic valve closure was determined from a vibration on the LA pressure curve, which coincides exactly with the aortic pressure tracing notch (Figure 1). The mitral valve opening corresponds to the LA and LV pressure crossover. On pressure tracings with high gain (Figure 2) the isovolumic relaxation time was measured from the lowest point of the negative LV dP/dt signal to the LV and LA pressure crossover. The LA pressure pulse was defined as the difference between the highest and the lowest LA pressure. For statistical evaluations the Student paired t test was used. A p value of <0.05 was considered statistically significant.

### RESULTS

LV and LA pressures measurements and first derivatives at rest and during the first 30 seconds of left anterior descending balloon occlusion in 32 patients are list-

The LV peak systolic pressure decreased from 135 ± 12 to  $106 \pm 9$  mm Hg (p < 0.01) simultaneously with a decrease of LV max dP/dt from 1,634 ± 136 to 1,137 ± 127 mm Hg/s (p <0.01). An increase of LV enddiastolic pressure from  $12 \pm 2$  to  $37 \pm 3$  mm Hg (p <0.001) and of LA mean pressure from 11  $\pm$  2 to 29  $\pm$ 2 mm Hg (p <0.001) was noted. There was a difference between LV end-diastolic pressure and LA mean pressure of 1.5 mm Hg at rest and 7.8 mm Hg after 30 seconds of left anterior descending occlusion. The LA max dP/dt increased from 177  $\pm$  13 to 381  $\pm$  21 mm Hg/s (p <0.001) and LA pressure amplitude (LA pulse pressure) from  $16 \pm 3$  to  $26 \pm 4$  mm Hg (38% increase) (p <0.05). LA A wave pressure increased from  $20 \pm 5$  to  $55 \pm 6$  mm Hg (p <0.01) during ischemia (Figure 3).

LV and atrial volumes with the corresponding pressure parameters in 10 patients studied with cineangiography are listed in Table II. Left end-diastolic volume index increased within the first 30 seconds of left anterior descending occlusion from  $75 \pm 7$  to  $102.5 \pm 10$  ml/ m<sup>2</sup> (26%) (p <0.001). LV end-systolic volume index increased from 30  $\pm$  5 to 59  $\pm$  9 ml/m<sup>2</sup> (31%) (p <0.001) during acute ischemia, while LV stroke volume

FIGURE 1. Left atrial (LA) and left ventricular (LV) pressures recorded at rest. Aortic valve closure (AOVC) corresponds to the notch on the V wave and the mitral valve opening (MVO) to the second notch corresponding (crossover of the LV and LA pressure curves). Isovolumic relaxation time (IVRT) can easily be calculated from AOVC to MVO.

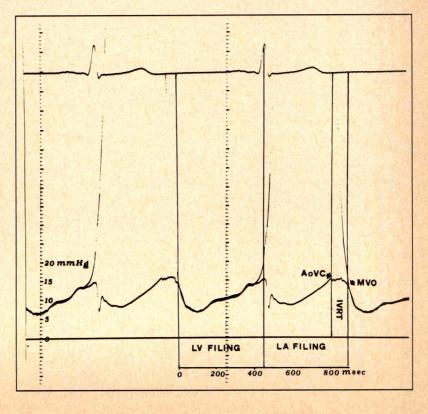


TABLE I LV and LA Pressures During Left Anterior Descending Occlusion\*

					MA DESCRIPTION OF THE	Estate Land
	Occlusion (seconds)					
	Rest	7	14	21	30	Pts (n)
LV PSP (mm Hg)	135 ± 12	133 ± 12	124 ± 11	115 ± 10	106 ± 9	32
LV EDP (mm Hg)	12 ± 2	14±3	22 ± 3	30 ± 4	37 ± 3	32
LA mean (mm Hg)	11 ± 2	12±2	16±2	22 ± 3	29 ± 2	32
LV max dP/dt (mm Hg/s)	$1,634 \pm 134$	$1.576 \pm 146$	$1,408 \pm 265$	$1.298 \pm 139$	$1.137 \pm 127$	32
LA max dP/dt (mm Hg/s)	$177 \pm 13$	$195 \pm 16$	253 ± 22	324 ± 23	381 ± 21	32
LVEF (%)	61 ± 7				42 ± 2	10
LA contribution to LVSVI	26 ± 5				57 ± 4	10

\* Hemodynamic values and contractility indexes of the 32 patients.

EDP = end-diastolic pressure; EF = ejection fraction; LA = left atrial; LV = left ventricular; mean = mean pressure; PSP = peak systolic pressure; SVI = stroke volume index.

	LV PSP				LVV						LAV	LA	
	(mm Hg)	LA	LA		pre				LA	LA	pre	Contrib	LAA
	LV EDP	Mean	PULS P	LVEDVI	A	LVESVI	LV	LVSVI	MAX	MIN	Α	to LVSVI	vol
Pt	(mm Hg)	(mm Hg)	(mm Hg)	$(ml/m^2)$	$(ml/m^2)$	$(ml/m^2)$	EF (%)	$(ml/m^2)$	$(ml/m^2)$	$(ml/m^2)$	$(ml/m^2)$	(%)	(ml/m <sup>2</sup>
1 R	135/12	11	15	71	59	29	61	43	41	17	30	30	24
1	105/36	30	23	95	73	56	41	39	63	26	54	72	37
2 R		9	13	69	57	24	65	45	39	15	27	27	24
1	93/32	28	21	92	72	52	43	40	61	30	52	55	31
3 R	147/15	13	18	81	72	33	59	48	42	18	27	19	24
- 1	108/38	31	29	115	95	69	40	46	69	31	57	57	38
4 R	125/9	7	12	73	62	30	59	43	39	17	29	28	22
- 1	95/36	30	24	104	87	61	42	44	60	32	51	43	28
5 R	152/13	11	18	80	68	33	59	47	41	18	30	26	23
- 1	112/39	30	28	110	95	65	41	45	65	25	56	47	30
6 R	131/13	11	16	82	74	40	51	42	43	17	28	26	26
- 1	102/41	33	27	116	95	67	42	49	67	30	56	53	37
7 R	112/8	7	12	72	62	28	61	44	41	19	30	25	22
-1	95/36	30	24	97	75	45	43	42	65	31	58	64	34
8 R	128/12	10	17	89	78	33	63	56	45	20	31	20	25
-1	102/41	33	29	112	97	70	38	42	70	33	53	52	37
9 R	151/16	13	18	71	57	29	59	42	45	20	35	36	25
-	120/39	31	25	93	73	51	45	42	69	30	56	62	39
0 R	133/12	10	17	69	61	25	78	54	36	18	26	22	18
- 1	108/37	29	28	91	70	51	44	40	58	24	50	65	34
R	133/12	10.2	15.6	75.7	65	30.4	61.5	46.4	41.2	17.9	29.3	25.9	23.3
	±13/±2.5	±2.1	±2.4	±6.8	±7.5	±4.6	±6.8	±4.9	±2.8	±1.5	±2.6	±5	±2.3
- 1	104/37.5	30.5	25.8	102.5	83.2	58.7	41.9	42.9	64.7	29.2	54.3	57	34.5
	±8.5/±2.7	±1.6	±2.8	±10	±11.5	±8.8	±2	±3.1	±4.1	±3.1	±2.7	±8.8	±3.7
value	e<0.001/0.001	0.001	0.001	0.001	0.05	0.001	0.05	NS	0.001	0.001	0.001	0.001	0.001

EDVI = end-diastolic volume index; ESVI = end-systolic volume index; I = ischemia; LVV pre A = left ventricular volume before left atrial contraction; MAX = maximum volume; MIN = minimum volume; Pre A = volume before A wave; vol = volume. Other abbreviations as in Table I.

index diminished from  $46 \pm 5$  to  $43 \pm 3$  ml/m<sup>2</sup> (difference not significant) and LV ejection fraction from 61.5  $\pm$  7 to 42  $\pm$  2% (31% reduction) (p <0.05). LA volume before mitral valve opening (LA volume max) increased from  $41 \pm 3$  to  $65 \pm 4$  ml/m<sup>2</sup> (36%) (p <0.001) and LA minimal volume (volume after LA contraction) from  $18 \pm 2$  to  $29 \pm 3$  ml/m<sup>2</sup> (37%) (p <0.001). There was an augmentation of both LA volume before LA contraction from 29  $\pm$  3 to 54  $\pm$  3 ml/m<sup>2</sup> (46%) (p <0.001) and the LA volume amplitude (stroke volume) from  $23 \pm 2$  to  $34.5 \pm 4$  ml/m<sup>2</sup> (37%) (p <0.001). The contribution of LA contraction to LV stroke volume index, increased from  $26 \pm 5$  to  $57 \pm 9\%$  and isovolumetric relaxation time increased from  $82 \pm 7$  to  $96 \pm 6$  ms (p <0.05). Isovolumetric relaxation time started to shorten 14 ± 6 seconds after left anterior descending occlusion, reaching 57 ± 5 ms after a 30-second occlusion; this was accompanied by a reduction of LV peak

negative dP/dt. The shortening of isovolumetric relaxation time phenomenon could be substantiated from the observation of valve movement during contrast injec-

### DISCUSSION

Myocardial ischemia is known to cause myocardial dysfunction. We have observed a dramatic reduction of LV peak negative dP/dt after the first seconds of acute myocardial ischemia during balloon occlusion during percutaneous transluminal coronary angioplasty<sup>19</sup>; these observations are in accordance with animal studies<sup>20</sup> and have been confirmed by other investigators in studies of humans.21 Very little, however, is known about the LA function during acute ischemia.

Our observations have shown an inverse relation between LV and LA performance during LV ischemia. While LV peak systolic pressure and dP/dt max decreased by 25 to 30%, respectively, LA mean pressure and LA contractility increased significantly (105% increment of LA max dP/dt). The diminution of the LV ejection fraction of 32% during ischemia was counterbalanced by an increased LA booster function resulting in a remarkable augmentation of LV end-diastolic volume. Thus, the LV stroke volume remains almost constant despite a dramatic reduction of the ejection fraction.

These results confirm previous observations reported by Rahimtoola et al<sup>16</sup> and Matsuda et al,<sup>12</sup> who noted an increase in LA contraction in animals during LA stretching by volume load. Other observations by Payne et al<sup>17</sup> and Braunwald and Frahm<sup>15</sup> also suggested that the Frank-Starling mechanism plays an important role when LA volume is increased with blood transfusions.

Neurohumoral factors may influence LA contractility. Since neither atrial peptides nor catecholamines have been measured in our study, the role of these factors remains unclear. The absence of significant heart rate changes during ischemia renders an important role of catecholamines unlikely. In animal experiments Sasayama et al<sup>11</sup> noted that atrial myocardial shortening was remarkably enhanced during experimental mitral regurgitation, with an increase of atrial diameter leading to the appearance of a prominent atrial A wave. In our study the contraction amplitude of the left atrium

increased significantly during LV ischemia, augmenting its contribution to the LV stroke volume index from 26  $\pm$  5 to 57  $\pm$  9%. Furthermore, the LA max dP/dt doubled during LV ischemia, suggesting enhanced LA contractility. This phenomenon is clinically known as the prominent "atrial kick." The LA kinetics may protect the pulmonary circulation from excessive pressure increase during ischemia. After 30 seconds of occlusion, LV end-diastolic pressures significantly surpassed the mean atrial pressure; this phenomenon has also been observed in other states of LV failure. The LA booster pump action appears to become an important factor in forcefully filling the LV chamber, which is stiffened under ischemic conditions. During atrial contraction only a minor amount of blood is ejected into the pulmonary venous circulation. Since in our model the left atrium was not affected by ischemic events, the even more generous contraction may prevent important backflow into the pulmonary venous system as observed in ventricular hypertrophy with diminished ventricular end-atrial compliance. 18 A different pathologic mechanism affecting both the atria and the ventricles may explain the lack of correlation between mean LA pressure and mean LA volume in patients with valvular heart disease.<sup>13</sup> In our study we noted an excellent correlation between LA pressure, LA pulse pressure and LA volume; these parameters simultaneously increased during

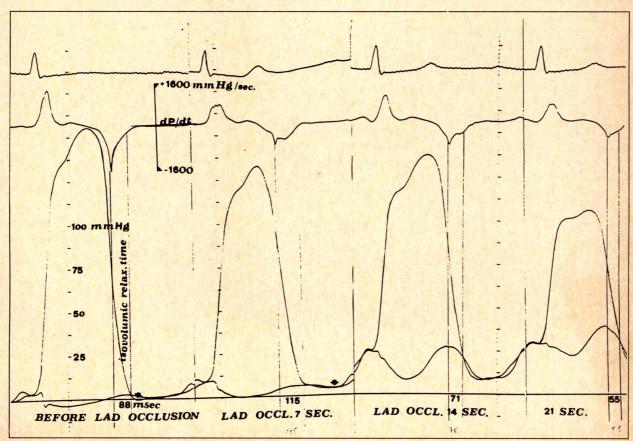


FIGURE 2. Simultaneously recorded left atrial and left ventricular pressures with left ventricular first derivative at rest and during left anterior descending (LAD) occlusion (OCCL). The earliest phenomenon is a shortening and a deformation of the negative dP/dt signal with the lowest point of the LV diastolic pressure shifting into mid-diastole (arrow) simultaneous to a prolongation of isovolumic relaxation time.

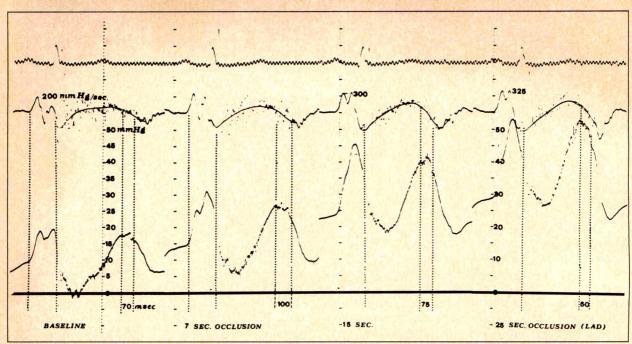


FIGURE 3. Left atrial pressure recorded at rest and during left anterior descending (LAD) occlusion with left atrial first derivative. During acute ischemia there is left atrial pressure increase (prominent A wave) with LA max dP/dt increase and shortening of the isovolumic relaxation time.

acute ischemia, since the LA myocardium reacts physiologically to the increased load. The shortening of the isovolumic relaxation period during advanced ischemia is a byproduct of our study and is discordant with previous studies. 22,23 Prolongation of the isovolumic relaxation period is a transient phenomenon during the early phase of ischemia. LV global relaxation is severely impaired during transient coronary occlusion, as shown in Figure 2; the lowest diastolic pressure point invariably moves to the right toward mid-diastole. As LA pressure increases, the mitral valve opens earlier; this upward shift of the LA pressure curve causes the abbreviation of isovolumic relaxation.

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## Alcohol Consumption, Serum Lipids and Severity of Angiographically Determined Coronary Artery Disease

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The relation of alcohol consumption to serum lipids and the severity of coronary atherosclerosis was examined in 212 men undergoing coronary angiography. The severity of coronary atherosclerosis was assessed in terms of the presence of ≥75% diameter stenosis and the Gensini severity score. Alcohol consumption was divided into 4 categories: none (0 ml alcohol/week), light (1 to 100 ml alcohol/week), moderate (101 to 300 ml alcohol/week) and heavy (≥301 ml alcohol/week). Alcohol consumption was positively related to high-density lipoprotein cholesterol and inversely related to total cholesterol, but was not associated with triglyceride. After adjustment for these serum lipids as well as for cigarette smoking and systemic hypertension, the risk of coronary stenosis was significantly decreased in the moderate drinkers. A decreased risk among moderate drinkers also was noted in terms of Gensini's severity score. These findings suggest that moderate alcohol consumption may protect against severe coronary atherosclerosis. (Am J Cardiol 1990;65:287-289) The relation between alcohol consumption and coronary artery disease (CAD) has been a matter of controversy. Several epidemiologic studies have reported a negative association of alcohol consumption with CAD, while others have shown no association. Furthermore, an increased risk of CAD has been suggested in some studies. Few studies have examined the relation between alcohol consumption and angiographically defined CAD. It would be of particular interest to determine whether alcohol consumption is related to the severity of CAD in a Japanese population living in Japan who are at low risk of CAD. We examined the relation between alcohol consumption and the severity of angiographically determined CAD.

#### **METHODS**

Subjects: The study subjects were chosen from patients undergoing diagnostic coronary angiography for suspected or known CAD at Fukuoka University Hospital from April 1986 to March 1989. The following patients were excluded from the study: those having cardiac disease such as valvular disease, heart muscle disease, acute or old myocardial infarction or having undergone procedures such as coronary artery bypass grafting or percutaneous transluminal coronary angioplasty; those with conditions that influence serum lipids, fasting blood sugar, uric acid and plasma fibrinogen concentrations; patients with severe hepatic dysfunction or uncontrolled diabetes mellitus; and those receiving lipid-lowering agents, diuretics or clofibrate. Also excluded were those who had drunk alcohol in the past but did not currently drink it.

Determination of coronary atherosclerosis: Coronary angiography was performed by either the Judkins or Sones technique, and multiple views of all vessels in the left anterior oblique, right anterior oblique and posteroanterior view were recorded. The angiograms were interpreted by 3 experienced investigators. The right, left anterior descending and circumflex coronary arteries were evaluated and judged to be normal (0% obstruction), or 25, 50, 75, 90 or 99% obstructed according to the maximum obstruction in any projection. Arteries were defined as being involved if ≥75% diameter stenosis was present. Gensini's severity score,<sup>5</sup> a measure of the extent of CAD, was calculated.

Information on coronary risk factors: Information on drinking and smoking habits was extracted from the medical record. The current alcohol consumption was estimated from the consumption frequency and amount consumed of different alcoholic beverages by using the

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	Alcohol Consumption						
Serum Lipid (mg/dl)	None (n = 58)	Light (n = 21)	Moderate (n = 80)	Heavy (n = 53)	p Value for Trend		
Total cholesterol	205 ± 5	196 ± 8	189 ± 4	190 ± 5	0.02		
Triglyceride	145 ± 9	$118 \pm 14$	130 ± 8	124±9	0.12		
HDL cholesterol	$37 \pm 1$	$38 \pm 2$	$41 \pm 1$	42 ± 1	0.01		

<b>TABLE II</b> Relation Between Alcohol Consumption and Frequency of Hypertensives and Frequency of Smokers									
	Alcohol Consumption								
	None (n = 58)	Light (n = 21)	Moderate (n = 80)	Heavy (n = 53)					
Smokers (%) Hypertensives (%)	61 39	77 59	80 36	79 39					

alcohol concentration of each beverage (4.5% for beer, 43% for whiskey, 12% for sake and so on). The level of alcohol drinking was divided into 4 categories: none (0 ml), light (1 to 100 ml/week), moderate (101 to 300 ml/week) and heavy (≥301 ml/week). The amount of cigarette smoking was also obtained from self-reported information. Those who had not smoked for ≥5 years were defined as nonsmokers.6 Those who had a systolic blood pressure of ≥160 mm Hg or diastolic ≥95 mm Hg, or both, and those under treatment for hypertension were defined as hypertensive. Body mass index was expressed as weight (kg)/height (m<sup>2</sup>). Overnight fasting venous blood was taken for measurement of total cholesterol, triglyceride, high density lipoprotein cholesterol, uric acid and fasting blood sugar. 11 Plasma fi-

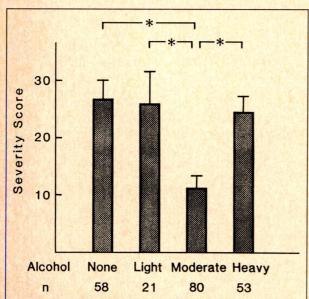


FIGURE 1. Adjusted means of Gensini's severity score according to categories of alcohol consumption. Analysis of covariance was controlled for age, total cholesterol, triglyceride, high-density lipoprotein cholesterol, cigarette smoking and hypertension. \* p <0.05.

**TABLE III** Adjusted Relative Risk of Coronary Stenosis According to Drinking Levels and 95% Confidence Intervals

	Alcoho	I Consumption	on		
No. of Stenotic Vessels	None	Light	Moderate	Heavy	
0	23	7	58	24	
1-3	35	14	22	29	
Relative risk	1.00	1.22 (0.40–3.71)	0.29 (0.13–0.63)	1.12 (0.48–2.63)	

Adjusted for age, total cholesterol, triglyceride, high density lipoprotein cholesterol, cigarette smoking and hypertension.

bringen concentration was also determined by the method of Swain and Feders. 12

Statistical procedures: The association between alcohol consumption and CAD was assessed by analysis of covariance and logistic regression analysis. In the logistic regression analysis, CAD was defined as being present if any of the 3 arteries was ≥75% narrowed. Relative risks were the antilogarithms of logistic regression coefficients, and 3 indicator variables were given to the levels of alcohol consumption. Their 95% confidence intervals were calculated from the standard errors of the regression coefficients. Among the independent variables (except for alcohol intake), smoking and hypertension were treated as dichotomous variables and the others as continuous variables. Statistical analyses were performed by the Statistical Analysis System (SAS).<sup>13</sup>

### RESULTS

A total of 212 subjects were selected for the analysis, excluding those with occlusion of the left main coronary artery. One hundred twelve subjects had clear coronary arteries, and 29% of them had ergonovine-induced spastic angina. The average age ± standard deviation of the 4 groups was  $60 \pm 9$  years for nondrinkers and  $55 \pm 9$ ,  $56 \pm 11$  and  $56 \pm 9$  for light, moderate and heavy drinkers, respectively.

Age-adjusted serum lipid concentrations are listed in Table I. Total cholesterol was decreased and high-density lipoprotein cholesterol was increased with increasing levels of alcohol consumption, while no significant relation was noted for triglyceride levels.

Table II lists the frequency of smokers and hypertensives according to the levels of alcohol consumption. There are higher proportions of smokers in the drinkers than in the nondrinkers. The highest proportion of smokers was found in the moderate group and the lowest in the nondrinking group. The lowest proportion of hypertensives was also found in the moderate group. The association of alcohol consumption with other coronary risk factors was also examined, but there was no apparent relation between alcohol consumption and factors such as body mass index, fasting blood sugar, uric acid and fibrinogen.

The net association between alcohol consumption and severity of CAD was examined, with the 3 serum lipids, smoking and hypertension controlled. Figure 1 shows the results of analysis of covariance, and Table III lists the relation between alcohol consumption and

CAD in terms of relative risk. Both Gensini's score and the relative risk were significantly decreased only at the level of moderate consumption. Multivariate analysis adding all other risk factors (body mass index, fasting blood sugar, uric acid and fibrinogen) produced essentially the same relation between alcohol consumption and CAD.

### DISCUSSION

Coronary angiography was first used by Barboriak et al<sup>14</sup> to examine the association between alcohol consumption and coronary artery occlusion. They found a statistically significant inverse relation between alcohol consumption and CAD scores, which continued to the highest consumption level (≥180 ml/week) when the analyzed patients were undergoing coronary angiography. Gruchow et al15 also found an inverse relation up to a much higher level of alcohol consumption (≥300 ml/week). Pearson et al16 demonstrated an inverse association between CAD and the frequency of alcohol consumption in women but not in men. Contrary to these previous studies, the present study did not observe a continuous inverse relation between alcohol consumption and CAD. Nevertheless, we found a clear evidence of a decreased risk among moderate drinkers. Such a relation was also supported by prospective studies<sup>17</sup> that examined the incidence of mortality from CAD. The reason for this discrepancy between the previous studies and the present study is not clear. Men who have been diagnosed as having CAD or men who had an angina attack are likely to have reduced or stopped their alcohol intake. Such a change in drinking habits due to disease status may erroneously produce a decreased risk among moderate drinkers, but those subjects were excluded from the present study. Some selection is possible for persons undergoing coronary angiography. If persons with normal coronary arteries undergo coronary angiography due to alcohol-related conditions such as spastic angina, the risk of CAD would be attenuated. Men drinking a large amount of alcohol may differ from moderate drinkers in their characteristics so that the protective effect of alcohol, if any, may be balanced by the elevated risk due to other factors associated with heavy drinking.

Several mechanisms have been postulated for the inverse relation between alcohol consumption and CAD. Previous investigators have hypothesized that the protective effect of alcohol is mediated by elevated high density lipoprotein cholesterol and decreased blood pressure. 18 We demonstrated a decreased risk among moderate drinkers after adjustment for these risk factors. This finding suggests that alcohol may exert its effects by another mechanism independent of both high density lipoprotein cholesterol and hypertension. Although it has not been proven, moderate alcohol consumption may reduce the effect of psychological stress on the individual. Stress has been implicated as a possible risk factor in CAD. 19 Furthermore, alcohol may exert an inhibitory effect on platelet aggregation and reduce plasma fibrinogen and increase fibrinolytic activity. 20,21 Since the results of animal studies have demonstrated that alcohol intake reduces the formation of atheromatous plaque,<sup>22</sup> moderate alcohol consumption may protect against atherosclerosis by inhibition of atheromatous plaque formation.

In the present study, no significant increase in triglyceride related to alcohol consumption was observed, in contrast with a previous study.<sup>23</sup> The reason for this difference is not clear, but Ginsberg et al<sup>24</sup> found a significant triglyceride increase after ethanol ingestion in hypertriglyyceridemic subjects but not in normal subjects. Low basal triglyceride levels in our study might have contributed to the absence of an increase in triglyceride. Furthermore, these results indicate that changes in high-density lipoprotein cholesterol are independent of the triglyceride changes.

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## Lack of Correlation Between Transient Myocardial Ischemia and Late Potentials on the Signal-Averaged Electrocardiogram

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The relation between transient myocardial ischemia and late potentials was investigated in 100 patients with coronary artery disease who underwent serial recordings of the signal-averaged electrocardiogram before, during and after dipyridamole infusion. During this test, 47 patients (group 1) developed transient myocardial ischemia (with ST elevation in 14 cases and ST depression in 33), whereas 53 patients (group 2) did not. Baseline signalaveraged electrocardiogram was abnormal in 20 patients (20%): a QRS duration >115 ms was seen in 6 patients, a late potential (root mean square voltage of last 40 ms of QRS [RMS40]  $<25 \mu V$ ) in 9, both abnormalities in 5, with no significant differences between groups 1 and 2 (26 vs 15%, respectively). In both groups, comparison of recordings obtained before, during and after dipyridamole test revealed no significant changes in QRS duration and RMS40. Absence of significant differences was also observed when patients with transient ischemic ST elevation or ST depression were examined separately. During the test, 100% of abnormal basal recordings remained abnormal and 98% of normal recordings remained within normal limits. In only 2 patients (from group 1) RMS40, which showed borderline values at baseline, decreased to abnormal values during dipyridamole test. These data suggest that electrophysiologic abnormalities induced by transient myocardial ischemia may not bear any relation with the substrate for chronic reentrant ventricular tachyarrhythmias, as reflected by late potentials on the signal-averaged electrocardiogram.

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elayed and fractionated activation potentials were initially recorded from ischemic regions of the canine heart, where they provided the electrophysiologic basis for reentrant ventricular rhythms. 1,2 Endocardial and epicardial late potentials appeared to correspond to low-amplitude, high-frequency signals detected at the end of QRS on the body surface signalaveraged electrocardiogram.3-5 Late potentials on the signal-averaged electrocardiogram were found to correlate with the occurrence of spontaneous and electrically induced ventricular tachyarrhythmias in patients with ischemic heart disease and prior myocardial infarction. 6-10 On the other hand, evidence for a link between transient myocardial ischemia and late potentials is missing. In the present report, the correlation between transient myocardial ischemia and late potentials was prospectively sought in a series of 100 patients with coronary artery disease, by analyzing serial recordings of the signal-averaged electrocardiogram obtained before, during and after provocation of ischemia. To induce transient myocardial ischemia and maintain an optimal ambient noise for signal averaging, we used intravenous dipyridamole infusion. 11-13

#### **METHODS**

Population: Criteria for inclusion in this study were: (1) an established diagnosis of coronary artery disease and myocardial infarction, based on history, electrocardiographic and enzymatic criteria, or angina, based on history of typical chest pain at rest or during effort, associated with transient ischemic ST changes on 12-lead, ambulatory or exercise electrocardiogram; (2) a QRS duration <120 ms with absence of bundle branch block pattern on the surface electrocardiogram; (3) absence of recent electrolyte imbalance, antiarrhythmic or  $\beta$ blocker drug treatment, acute or chronic heart failure; and (4) patient consent to undergo the study protocol. A total of 100 consecutive patients admitted to our hospital between January and September 1989 met these inclusion criteria and entered the study. This group consisted of 85 men and 15 women, with a mean age ± standard deviation of  $58 \pm 9$  years (range 34 to 77).

Study design: All patients underwent dipyridamole testing and serial recordings of the signal-averaged electrocardiogram. Cardiac catheterization was performed in 73 of the 100 study patients (73%) within 15 days of the test. Dipyridamole testing was performed according to a previously described protocol, <sup>12</sup> after withdrawal of all therapy for ≥24 hours. The protocol consisted of the

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intravenous administration of dipyridamole at the dose of 0.56 mg/kg body weight over 4 minutes, followed by an observation period of 4 minutes; a "high" dose of additional 0.28 mg/kg over 2 minutes was used when the "low" dose failed to induce ischemic ST changes. After an observation period of 4 minutes, aminophylline was administered intravenously at the dose of 240 mg over 2 minutes, to prevent any further effects of dipyridamole. Aminophylline was also used to relieve myocardial ischemia in case of a positive result after the low dose. A 12-lead electrocardiogram was obtained at baseline, after infusion of the low dipyridamole dose, before infusion of the high dose when appropriate, and before and after infusion of aminophylline. During the test, the tracing in leads X, Y and Z was continuously monitored. Endpoints of the test were completion of the protocol or induction of transient ischemic ST changes. The latter were defined as transient ST elevation or rectilinear or downsloping ST depression ≥1 mm from baseline or from the control level in case of resting ST abnormalities, recorded in ≥1 conventional electrocardiographic lead other than aVR and lasting ≥1 minute.

Signal-averaged electrocardiography: Recordings were carried out with a commercially available machine (Arrhythmia Research Technology 1200 EPX unit), using previously reported techniques.<sup>6</sup> The electrocardiogram was recorded with standard bipolar X, Y and Z leads. Signals were amplified, averaged and filtered with a bidirectional filter at frequencies of 25 to 250 Hz. The filtered leads were then combined into a vector magnitude  $\sqrt{X2 + Y2 + Z2}$  and the QRS duration and root mean square voltage of the signals in the last 40 ms of QRS (RMS40) were calculated. The duration of low amplitude signals ( $<40 \mu V$ ) was also measured but not used for analysis. A baseline, or pretest, signalaveraged electrocardiogram was obtained immediately before administration of dipyridamole; the recording was then repeated after infusion of the low dose, after infusion of the high dose when appropriate and after infusion of aminophylline. The last was defined as the posttest recording. In each patient, recordings were accepted for analysis only if the noise level was ≤0.8 µV and showed a  $\leq 0.2 \,\mu\text{V}$  difference between all of them. The time interval between the various steps of the dipyridamole test protocol (4 minutes) always allowed collection of the number of beats (usually between 200 and 400) necessary to reach the endpoint noise level before entering the next step. The study design also required verification that the ST level on the 12-lead electrocardiogram was comparable (<1 mm difference) at the beginning and the end of each signal-averaged electrocardiographic recording. An abnormal signal-averaged electrocardiogram was defined as a recording showing a QRS duration >115 ms, a RMS40 <25  $\mu$ V, or both. 14 Late potentials were defined as signals with abnormal RMS40.6

Cardiac catheterization: Cardiac catheterization was performed using the Judkins technique. Selective coronary angiograms were recorded in multiple views and left ventriculograms in the right anterior oblique view. Coronary stenoses were judged to be significant if the reduction in luminal diameter was >50%. Left ven-

tricular ejection fraction was calculated according to the area-length method. Left ventricular wall motion abnormalities, defined as the presence of segmental akinesia or dyskinesia, were evaluated using a 5-segment model, which divided the ventricular outline into an anterobasal, an anterolateral, an apical, an inferior and a posterobasal segment.<sup>15</sup>

Statistical analysis: Patients were divided into 2 groups, according to the outcome of the dipyridamole test. Group 1 included patients in whom the test was positive for transient myocardial ischemia and was further divided into 2 subgroups, based on the presence of transient ST elevation (group 1A) or ST depression (group 1B) during dipyridamole-induced myocardial ischemia. Group 2 comprised patients in whom the test was negative. Values of the signal-averaged electrocardiogram parameters on serial recordings performed before, during and after the test were compared using analysis of variance and the Student t test for paired data. A p value <0.05 was considered statistically significant. All variables are mean  $\pm$  standard deviation.

#### RESULTS

Dipyridamole test: Among the 100 study patients, 47 (group 1) developed transient myocardial ischemia during the dipyridamole test, while 53 (group 2) did not show this phenomenon and served as a control group. No complications were noted during the tests. Clinical, electrocardiographic and angiographic variables of patients in groups 1 and 2 are listed in Tables I and II, respectively. Group 1 comprised 19 patients with recent (<3 weeks) myocardial infarction (of which 8 had angina early after infarction) and 28 with angina (17 with and 11 without prior myocardial infarction). Significant stenoses of ≥1 major coronary artery were present in 40 of 41 patients who underwent coronary angiography. Dipyridamole-induced ischemia appeared after infusion of the low dose in 17 cases, and after the high dose in an additional 30 cases; it was symptomatic in 44 cases and silent in the remaining 3. Transient ischemic ST changes consisted of ST elevation in 14 patients and ST depression in 33; these changes were similar to those documented during spontaneous or exercise-induced ischemia in 32 cases. Group 2 included 35 patients with recent myocardial infarction (of which 1 had angina early after infarction), 5 asymptomatic patients with prior myocardial infarction and 13 patients with angina (7 with and 6 without prior myocardial infarction). Significant stenoses of ≥1 major coronary artery were present in 28 of 32 patients who underwent coronary angiography. During the dipyridamole test, 2 patients complained of atypical chest pain, in the absence of ischemic ST changes.

**Signal-averaged electrocardiogram:** The baseline (pretest) signal-averaged electrocardiogram was abnormal in 20 of the 100 study patients (20%). A prolonged QRS duration was seen in 6 patients (6%), a late potential in 9 (9%) and both abnormalities in 5 patients (5%). The proportion of patients with an abnormal signal-averaged electrocardiogram at baseline was similar in patients with or without dipyridamole-induced ischemia (respectively: 12 of 47 [26%] vs 8 of 53 [15%], differ-

TABLE I Clinical, Electrocardiographic and Angiographic Characteristics of Patients with Dipyridamole-Induced Transient Myocardial Ischemia (Group 1)

						Corona	ry Angiographic Data				
		Diagnosis			ST Changes			% Ste	enosis		
Pt	Age (yrs), Sex	Recent MI	Prior MI	Angina	During Angina	EF (%)	LV A/Dyskinesia	LM	LAD	LC	Right
1A: Sub	group with tran	sient ST elevati	on during tes	it							
1	68, M	1	0	S	1,1	70	PB	0	0	0	100
2	61, F	A nonQ	0	S	1, A	85	0	0	85	50	0
3	60, M	Α	0	S	1.1	65	AL, AP	0	100	90	40
4	52, M	A nonQ	0	S	↑or↓, A	70	AB	0	100	0	60
5	53, M	A*	0	S	1. A	43	AL, AP	0	100	0	0
6	69. F	Α	0	S	1. A	_					
7	55, M	*	0	0	0	70	0	0	100	100	70
8	62, M	Α	0	0	0	55	AP	0	100	0	0
9	63. M	A*	0	O	0	65	AL, AP	0	85	0	0
10	58, M	AnonQ	0	0	Ö	70	AP	0	100	70	90
11	68. M	0	A	S	↑. A	41	AL, AP, I	0	100	0	99
	THE PERSON NAMED IN COLUMN TWO IS NOT THE OWNER.		A								
12	54, M	0		М	↑, A	63	AP	0	99	0	100
13	52, M	0	A nonQ	М	↑ or ↓, A	75	AL	0	90	80	60
14	71, M	0	Α	S	1, A	-		10 TA 11	-	_	10
CONTRACTOR OF THE PARTY OF THE	A LONG THE RESERVE THE PARTY OF	sient ST depres	- ALL CONTROL OF THE PARTY OF T								
1	42, M	A nonQ*	0	S	<b>1</b>	68	AL	0	100	90	0
2	69, F	A nonQ	1	S		_			_	_	-
3	42, M	*	0	0	0	72	0	0	0	0	35
4	56. M	*	0	0	0	47	0	0	0	50	60
5	65, M	A nonQ		0	0	67		0	100	90	0
6	64, M		0	0	0	70		0	50	85	40
7	74, F	A nonQ	i	Ö	O	56		0	80	0	40
8	69. M	I*	0	0	0	61	PB	0	30	0	100
9		THE PARTY OF THE P	0	0	0	The State of Contract of the C		0		0	
	51, F	A*			O .	38	AL, AP		100	- 34 Y 3 TY - 10	0
10	62, M	0	A*	M		72	0	0	100	0	0
11	52, M	0	Α	E		65	AL, AP	0	100	40	90
12	68, M	0	Dev.	M		68	AP, I	0	65	50	0
13	60, M	0		M		68	PB	0	0	0	100
14	59, M	0	A nonQ	M		75	0	0	95	0	0
15	53, M	0	A nonQ	M		64	AL	0	100	0	0
16	63, M	0	InonQ	M	į	68	PB	0	90	0	100
17	51, M	0	A	М		65	AL	0	95	0	0
18	59. M	0	Α	М		55	AL, AP	0	95	0	0
19	59, F	o	*	S		52	PB	0	90	40	100
20	65. M	0	I, A	M		53	AL, AP, PB	0	100	60	70
	The second secon									and the state of the	
21	59, M	0	I, A	M		68	AL, AP, PB	0	95	70	100
22	50, M	0		М		70		_			
23	58, M	0	0	М	The state of the s	70	0	0	70	40	0
24	51, M	0	0	M		70	0	0	50	40	100
25	64, M	0	0	M		70	0	0	90	80	0
26	58, F	0	0	M	57. III.	76	0	0	50	75	45
27	61, M	0	0	M		70	0	0	100	0	0
28	69. M	0	0	M		60	0	0	100	80	0
29	61, F	0	0	M		78	0	0	60	0	0
30	59, M	Ö	0	E	Time to	68	0	0	80	80	60
31	62. M	0	0	E		69	0	0	65	65	0
32	61, M	0	0	M		09			00	05	0
33	76, M	0	0	M		Wante !					100

ence not significant). Tables III and IV list mean values of the signal-averaged electrocardiogram parameters before, during and after the dipyridamole test. In group 1 (Table III), comparisons were made between the pretest recording, that obtained during ischemia (after the low dose in 17 cases and the high dose in 30), and the posttest recording. None of these comparisons revealed any significant differences regarding QRS duration, RMS40 or noise level. Absence of significant differences was also noted when cases with transient ischemic

ST elevation or depression were examined separately. In group 2 (Table IV), comparisons were made between the pretest recording, that obtained after the low dose (not listed in Table IV), that obtained after the high dose (Table IV) and the posttest recording. Once again, none of these comparisons found any significant differences concerning QRS duration, RMS40 or noise level. All 20 patients (100%) in groups 1 and 2 with abnormal QRS duration or RMS40 at baseline maintained abnormal values on all the subsequent recordings; similarly,

<sup>\*</sup> These patients with myocardial infarction were subjected to intravenous thrombolysis within 6 hours of the onset of chest pain.

† = elevation; ! = depression; A = anterior; AB = anterobasal; AL = anterolateral; AP = apical; E = exertional; EF = ejection fraction; ! = inferior; LAD = left anterior descending coronary artery; LM = left main trunk; LV = left ventricle; M = mixed; MI = myocardial infarction; PB = posterobasal; S = spontaneous; O = absent; — = not determined.

**TABLE II** Clinical, Electrocardiographic and Angiographic Characteristics of Patients Without Dipyridamole-Induced Transient Myocardial Ischemia (Group 2)

		Diagnasis			CT OL		ry Angiographic Data	0/ 5:			
	Age (yrs),	Diagnosis			ST Changes During	EF		% Ste	enosis		
Pt	Sex	Recent MI	Prior MI	Angina	Angina	(%)	LV A/Dyskinesia	LM	LAD	LC	Right
1	64, M	1	0	S	1			_	-	_	_
2	56, M	*	0	0	0	63	PB, I, AP	0	0	0	100
3	42, M	*	0	0	0	70	0	0	40	70	50
4 5	34, M	*	0	0	0	64	PB, I	0	0	0	100
6	64, M 61, F	*   ^ === O *	0	0	0	44	PB	0	0	0	100
7	59, M	A nonQ*	0	0	0	78	0	0	30	0	0
8	54, M	A nonQ A	i	0	0	68 54	AL AD AB	0	40	0	70
9	68, M	A*	0	0	0	60	AL, AP, AB AP	0	70 80	0	100
10	44, M	A*	0	0	0	35	AL, AP, I	0	30	0	0
11	46, M	A nonQ*	0	0	0	80	0	0	0	85	0
12	42, M	A*	0	0	0	53	AL, AP	0	100	0	65
13	38, M	*	0	0	0	55	AP, PB	0	75	100	0
14	61, M	1	0	0	0	58	Ar, rb	0	0	0	95
15	61, M	A nonQ	0	0	0	65	0	0	0	0	0
16	46, M	A	0	0	0	55	AP	0	70	0	100
17	42, M	1	0	0	0	50	I, PB	0	40	95	70
18	52, M	1	0	0	0	40	AP, I	0	0	60	0
19	56, M	A*	0	0	0	40	AL, AP	0	80	0	30
20	50, M	A*	0	0	0	65	AL, AP	0	100	90	0
21	59, M	A nonQ	0	0	0	75	AP	0	50	50	60
22	51, F	I nonQ*	0	0	0					_	
23	65, M	*	0	0	0	_					
24	62, F	*	0	0	0				_		
25	67, M	1	0	0	0		<u> </u>	<u> </u>			
26	41, M	A*	0	0	0						
27	53, M	Α	0	0	0	_			<b>77</b>		
28	68, M	Α	0	0	0	_	<u> </u>	_			
29	65, M	Α	0	0	0			_	_		
30	75, F	A nonQ	0	0	0	_	<u>-</u>	_		<u>.                                     </u>	
31	57, M	1	0	0	0		_	_		_	-
32	55, M	Α	0	0	0	-		-	-		-
33	59, F	1*	0	0	0			-	-	_	-
34	73, F		0	0	0	_ (		<del></del>	-	-	
35	52, M		1*	0	0	-		_	-		
36	57, M	0	A nonQ	S	1, A	63	AL, AP	0	90	0	0
37	62, M	0	HARLES	E	1	50	PB	0	70	0	90
38	63, M	0	No.	М		50	PB	0	30	100	100
39	48, M	0		M		70	1	80	70	70	70
40	52, M	0	Α, Ι	S		50	AP, I	0	90	90	100
41	60, M	0	1	M		60		0	70	60	100
42	66, M	0	A	S	†, A	_		ATT NOT	_		-
43	62, M	0	A, I	0	0	38	AL, PB	0	100	0	100
44	40, M	0	A 1	0	0	45	AL AD	0	0	0	60
45	57, M	0	A, I	0	0	40	AL, AP	0	100	60	100
46	50, M	0	A PARTY	0	0	100					ME PRO
47	61, M	0		0	0	75	_	_	-	_	_
48	38, F	0	0	S	1, A	75	0	0	40	0	0
49	70, M	0	0	M	↑ or ↓, I	75	0	0	70	65	60
50	59, M	0	0	E		69	0	0	80	40	50
51	77, M 65, M	0	0	M M			The second		100	7	
52											

\* Patients with myocardial infarction who were subjected to intravenous thrombolysis within 6 hours of the onset of chest pain. Abbreviations as in Table I.

78 of 80 patients (98%) with a normal baseline recording retained normal parameters during the dipyridamole test and afterwards. In only 2 patients from group 1 did RMS40 cross the boundary between normalcy and abnormalcy during the test: both patients had borderline RMS40 values at baseline (25.7 and 29.9  $\mu$ V), which lowered during dipyridamole-induced ischemia (21.6 and 24.1  $\mu$ V, respectively) and returned to normal

after the test (28.4 and 28.2  $\mu$ V, respectively). Figures 1 and 2 show 2 examples of serial recordings of the signal-averaged electrocardiogram during the dipyridamole test. Drug-induced myocardial ischemia was evident on the conventional electrocardiogram as ST elevation in Figure 1 and ST depression in Figure 2. However, there were no significant changes between the signal-averaged electrocardiogram recorded at baseline and that during

ischemia: both recordings were normal in Figure 1 and abnormal in Figure 2.

### DISCUSSION

Electrophysiologic changes associated with transient myocardial ischemia in patients with coronary artery disease are poorly understood. A study of the ability of ischemia to evoke late potentials on the signal-averaged electrocardiogram may provide insights into this issue. The dynamic nature of late potentials has been clearly demonstrated in the setting of acute myocardial infarction, when late potentials may wax and wane within a 48-hour period. 16

We undertook a prospective study to evaluate the effects of transient myocardial ischemia on signal-averaged electrocardiogram parameters. Baseline recordings

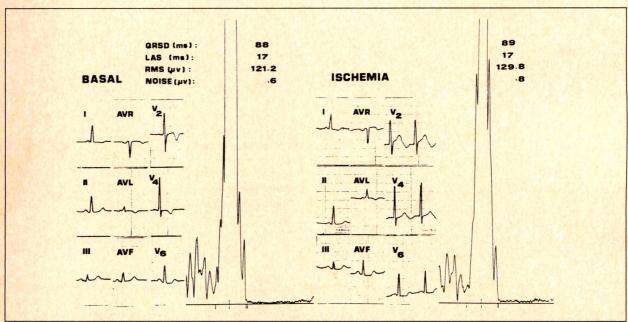


FIGURE 1. Conventional and signal-averaged electrocardiograms performed in patient 4 (group 1A) at baseline (left) and during dipyridamole-induced ischemia (right). The latter appears as transient ST elevation on the conventional tracing. The signalaveraged electrocardiogram is normal at baseline and does not show any significant changes during ischemia. LAS = duration of low amplitude signals  $<40 \mu V$ ; QRSD = high-frequency QRS duration; RMS = root mean square voltage of last 40 ms of QRS.

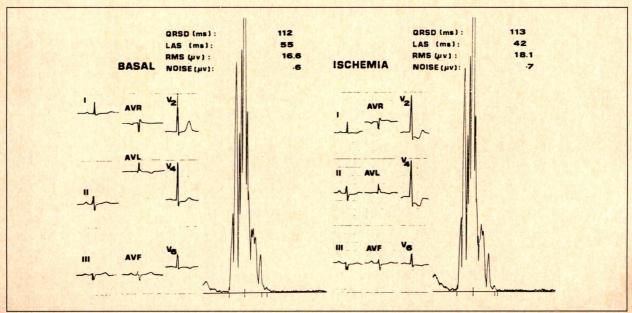


FIGURE 2. Conventional and signal-averaged electrocardiograms performed in patient 25 (group 1B) at baseline (left) and during dipyridamole-induced ischemia (right). The latter appears as transient ST depression on the conventional tracing.

The signal-averaged electrocardiogram is abnormal at baseline, due to the presence of a late potential, and does not show any significant changes during ischemia. Abbreviations as in Figure 1.

were compared with those performed during provocation of ischemia and after its resolution. Ischemia was induced by means of dipyridamole infusion. Studies of dipyridamole testing are exhaustive in showing that its diagnostic accuracy for coronary disease is excellent and similar to that of stress testing, when a "high" dose of 0.84 mg/kg is used.<sup>13</sup> For our purpose, induction of ischemia by dipyridamole offered the advantage of maintaining an optimal electrocardiographic signal-tonoise ratio, since the patients were resting in a supine position throughout the test. This enabled us to achieve baseline noise levels  $\leq 0.8 \,\mu\text{V}$  and a  $\leq 0.2 \,\mu\text{V}$  difference in noise level between all recordings performed in the same patient. Low noise levels are required to maximize both the chances for detection of late potentials<sup>17</sup> and the short-term reproducibility of the signal-averaged electrocardiogram in coronary artery disease. 18 Our experience confirms that the short-term stability of signalaveraged electrocardiogram parameters is high. 18 In fact, we did not find any significant differences in QRS duration and RMS40 on serial recordings obtained before, during and after dipyridamole infusion in the group without induced ischemia. These results were not influenced by the presence or absence of abnormal parameters at baseline. In our study population, the prevalence of an abnormal signal-averaged electrocardiogram (20%) was comparable to that reported in other studies of patients with coronary artery disease and without clinical ventricular arrhythmias.8,19-21

The most relevant finding in our study is that transient myocardial ischemia did not induce late potentials on the signal-averaged electrocardiogram. In fact, we were unable to detect any significant differences between recordings performed before, during and after dipyridamole infusion in the group with induced ischemia. The lack of significant effects of transient myocardial ischemia on the signal-averaged electrocardiogram was equally evident for the 2 phases of ischemia, namely its onset and peak and its resolution, as well as for its 2 types, expressed by ST elevation (transmural ischemia) or ST depression (subendocardial ischemia).<sup>22</sup>

Study limitations: Several technical and theoretical aspects need to be addressed. First, the sensitivity and specificity of dipyridamole tests for transient myocardial ischemia are by no means absolute. Our study population was selected among patients with documented coronary artery disease to lower the risk for false-positive tests. The possibility of a number of false-negative tests must be entertained; however, had any patients been misclassified in group 2, that would not have changed our results. In fact, they were concordant in groups 1 and 2 in showing no significant differences between serial recordings performed before, during and after dipyridamole infusion. Second, our analysis of the effects of ischemia on the signal-averaged electrocardiogram may have been perturbed by the use of drugs; this hypothesis is unlikely, since neither dipyridamole nor aminophylline significantly affected QRS duration or RMS40 in our control group of patients without induced ischemia. Third, the limitations of the signal-av-

**TABLE III** Values of Signal-Averaged Electrocardiogram Parameters on Serial Recordings Performed in 47 Patients with Dipyridamole-Induced Transient Myocardial Ischemia (Group I)

	Before Test	During Test	After Test
QRSD (ms)	102 ± 14	102 ± 11	102 ± 12
RMS40 (μV)	$64 \pm 47$	$66 \pm 54$	$60 \pm 44$
Noise (μV)	$0.5 \pm 0.2$	$0.6 \pm 0.2$	$0.6 \pm 0.2$

All values are mean ± standard deviation. QRSD = QRS duration; RMS40 = root mean square voltage of the last 40 ms of ORS.

**TABLE IV** Values of Signal-Averaged Electrocardiogram Parameters on Serial Recordings Performed in 53 Patients Without Dipyridamole-Induced Transient Myocardial Ischemia (Group 2)

	Before Test	During Test	After Test
ORSD (ms)	99 ± 13	98 ± 12	99 ± 13
RMS40 (μV)	67 ± 39	67 ± 39	$67 \pm 40$
Noise (µV)	$0.5 \pm 0.2$	$0.6 \pm 0.2$	$0.5 \pm 0.2$

All values are mean ± standard deviation. Abbreviations as in Table III.

eraging technique are well known.<sup>2</sup> A conduction delay in the ischemic myocardium with a Wenckebach pattern may not be amenable to a technique that requires that the signal of interest be repeated in a regular fashion. Finally, the fact that the duration of dipyridamoleinduced ischemia was approximately 4 minutes (observation time from the end of dipyridamole infusion to that of aminophylline) may have important implications. It may be speculated that ischemia induced in our study was not severe enough to evoke late potentials. On the other hand, equally short periods of ischemia may well precipitate complex ventricular arrhythmias. In fact, when arrhythmias occurred during spontaneous ischemic attacks, the time interval between the onset of ST changes and that of the arrhythmia averaged 3 minutes both in case of ST elevation<sup>23</sup> and ST depression.<sup>24</sup> In the present study, late potentials failed to appear during dipyridamole-induced ischemia, which was similar in type and duration to spontaneous ischemia. Thus, they may not provide an electrophysiologic basis for arrhythmias due to ischemic attacks, in patients with coronary artery disease. Experimental studies have revealed that several mechanisms may be responsible for ventricular arrhythmias in the acute stage of ischemia and after reperfusion of ischemic myocardium. Arrhythmias may be focal or reentrant in origin, and the pathways for reentry may differ in the acutely ischemic heart, with respect to the heart with chronic infarction; furthermore, slowing of conduction does not necessarily lead to fractionated activity. 1,2,25,26 The relevance of these mechanisms to the clinical setting is still conjectural. However, it may be suggested that electrophysiologic abnormalities secondary to transient myocardial ischemia in patients with coronary artery disease do not bear any relation with the substrate for chronic reentrant ventricular tachyarrhythmias, as reflected by late potentials on the signal-averaged electrocardiogram.

**Acknowledgment:** We are indebted to Mariella Montemaggiori, RN, for invaluable assistance throughout the study.

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### Detection and Localization of Tumor Necrosis Factor in Human Atheroma

Peter Barath, MD, PhD, Michael C. Fishbein, MD, Jin Cao, MD, James Berenson, MD, Richard H. Helfant, MD, and James S. Forrester, MD

Tumor necrosis factor (TNF) is a secretory product of normal macrophages that can cause cell necrosis, new blood vessel formation and thrombosis. These are also 3 characteristic features of the progression of stable atheroma to endothelial disruption. Accordingly, an immunohistochemical method was developed to detect TNF in human tissue. Using this method TNF positivity was demonstrated in 57 of 65 (88%) of tissue sections classified as atherosclerotic and in 5 of 11 (45%) sections classified as minimally atherosclerotic. TNF was absent in 6 sections classified as normal. TNF positivity was found not only in the cytoplasm of macrophages, but also in the cytoplasm and attached to the cell membrane of smooth muscle cells and endothelial cells of the human atheroma. Because TNF is known to cause new vessel formation, hemorrhagic necrosis and increased thrombogenecity, it may play a role in the evolution of uncomplicated to complex atheroma.

(Am J Cardiol 1990;65:297-302)

Tumor necrosis factor (TNF), which is produced principally by activated macrophages, <sup>1-6</sup> activates endothelial cells, <sup>7-10</sup> stimulates angiogenesis<sup>3</sup> and induces hemorrhagic necrosis. <sup>4,5</sup> Because central necrosis and new vessel formation in the presence of macrophage accumulation characterize evolving atheroma, <sup>11,12</sup> we hypothesized that TNF might be detected in these lesions. There are no published reports of morphologic localization of TNF; the purpose of this study, therefore, was to develop a method to detect and localize immunoreactive TNF in atherosclerotic human blood vessels, and to analyze its distribution in human atheroma.

### **METHODS**

We used arteries from freshly amputated legs and autopsies. There were 50 anterior and posterior tibial, femoral, carotid and coronary vessels. Exclusion criteria were coexisting neoplasia, immunologic disease and acute or chronic infectious diseases. Tissue was fixed in 10% neutral buffered formalin. Vessels taken from amputated legs were fixed within minutes of amputation; autopsy vessels were fixed within 6 hours. We made 82 sets of paraffin-embedded tissue sections: 12 from tibial arteries, 60 from coronary arteries and 10 from carotid and femoral arteries (Table I). Each set consisted of 6 consecutive sections. The first section was stained by hematoxylin and eosin, the second by immunohistochemistry for TNF, and then 4 sections were made for immunohistochemical identification of cell types. Each hematoxylin and eosin-stained section was classified as normal, having intimal thickening or being significantly atherosclerotic. We defined endothelial ulceration as rupture of the fibrous cap of the atheroma or presence of in vivo thrombus. Because postmortem change can cause loss of continuity changes on the endothelial surface, this finding alone was not defined as endothelial ulceration. The histologic classification was made independent of the subsequent immunohistochemical findings

We also performed immunohistochemical staining on a number of other tissue samples. As a positive control, we stained 5 necrotizing colon cancers obtained at surgical resection. As negative control we stained 5 samples from brain frontal lobe cortex.

Immunohistochemical identification of tumor necrosis factor: After deparaffinization and dehydration, the sections were incubated in 3% methanolic peroxidase for 10 minutes at room temperature, followed by trypsin digestion (0.1% of type III bovine pancreas trypsin in 0.5 M Tris buffer, pH 7.8) at 37°C for 10 minutes. Sections were incubated for 10 minutes in bovine serum

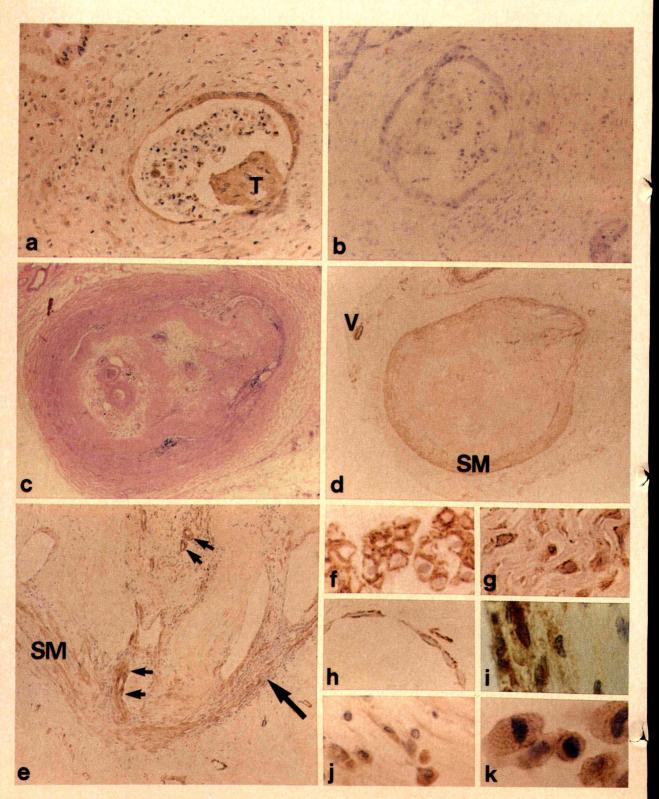
Address for reprints: Peter Barath, MD, PhD, Cedars-Sinai Medical Center, Division of Cardiology, 8700 Beverly Boulevard, Los Angeles, California 90048.

From the Division of Cardiology, Cedars-Sinai Medical Center, Los Angeles, California. Manuscript received June 7, 1989; revised manuscript received September 25, 1989, and accepted September 26.

diluted 1:20 in phosphate-buffered saline (PBS) (0.1 M phosphate-buffered 0.9% saline, pH 7.4) in a humidity chamber at room temperature.

The antiserum used for immunohistochemistry of TNF was a monoclonal antibody produced against recombinant human TNF-alpha (rhTNF) (gift of Dr. M. Narachi, Amgen). The antibody was purified with protein A-Sepharose chromatography. We used 1:1000 to

1:2000 dilution of the primary antibody with 1:20 swine serum:PBS and an incubation time of 30 minutes at room temperature in a humidity chamber. The secondary antibody, rabbit antiserum to mouse immunoglobulin G (Dako), was diluted to 1:50 with swine serum:PBS. After PBS washing we incubated the sections in swine antiserum to rabbit immunoglobulin G conjugated with horseradish peroxidase (Dako). Sections



were then washed in PBS and stained with 0.05% 3.3′-diaminobenzidine (DAB, Sigma). Sections were counterstained with hematoxylin. We used 4 types of negative controls: the primary TNF antiserum deleted from the staining procedure; the primary antiserum absorbed with excess rhTNF; the primary antiserum replaced with an antiserum produced in mouse but directed to rabbit immunoglobulin; and brain tissue (considered to be negative for TNF). We used necrotic colon carcinomas as positive controls, and corroborated the presence of TNF in these lesions by enzyme-linked immunosorbent assay (ELISA).

Immunohistochemical identification of cell types: The identity of individual cells within the atheroma was established by cell-specific immunohistochemical stains performed on sections adjacent to those stained for TNF.

For identification of macrophages HAM56 (Enzo Biochem Inc.), for vascular smooth muscle cells HHF35 (gift of Dr. A. M. Gown, Department of Pathology, University of Washington), and for T lymphocytes, Pan T (T11, Dako) monoclonal antibodies were used. For endothelial cells antihuman factor VIII-related rabbit antiserum (Dako) was used. For studies using monoclonal antibodies we used the above described system; for factor-VIII related antigen we used the PAP (peroxidase-antiperoxidase, Dako) system.<sup>14</sup>

Test of monoclonal antibody specificity: Human recombinant TNF alpha from 2 different sources (Amgen and T Cell Sciences, Inc.) underwent electrophoresis according to Laemmli. The bands were visualized with Coomassie brilliant blue. The proteins were transferred to nitrocellulose sheets in a Novex Western transfer apparatus (Novel). Immunoblotting was performed making cross-reaction between the rhTNF-s and monoclonal antibodies of 2 sources: Amgen (the antibody used in the immunohistochemical reactions) and T Cell Sciences.

**Enzyme-linked immunosorbent assay of vascular, tumor and brain tissue:** To establish that TNF was present in measurable quantity in tissues with TNF positivity, we extracted the protein from one of the colon tumors and from 2 of the carotid arteries that were immunohistochemically positive for TNF. The tissues were homogenized directly into 10% volume/weight of sodium dodecyl sulfate sample buffer containing 2%

TABLE I Frequency Distribution of Vessels and Sections
Analyzed

	Normal	Intimal Thickening	Arterio- sclerotic	Total
Coronary ar	rteries*	<b>计学或型层的</b> 体		
Arteries	2	5	27	34
Sections	2	5	53	60
Peripheral a	arteries			
Arteries	4*	6*	6 <sup>†</sup>	16
Sections	4*	6*	12 <sup>†</sup>	22
* Autopsy; † a	amputation.			

beta-mercaptoethanol. A commercially available TNF ELISA kit (Biokine, T Cell Sciences, Inc.) was used to measure the TNF concentration in the extracted tissue. The plates were read at varying time periods on a Perkin Elmer reader at 490 nm wavelength. Results were expressed in ng/mg wet weight. Data were analyzed with a Perkin Elmer analytical database software on a PC2 computer.

Induction of immunoreactive tumor necrosis factor expression by low density lipoprotein incubation in vascular smooth muscle cells in culture: Aortic smooth muscle cells (from normal human aorta collected from heart explant) were isolated by combination of collagenase (type CLS II) and elastase (type I) digestion and mechanical dissection. The cells were incubated in medium 199 containing 20% fetal bovine serum (both from Gibco) at 37°C. Confluent primary cultures were incubated with  $100 \mu g/ml$  LDL (Sigma) for 24 hours. Cultures without LDL incubation served as controls. The cultures were stained to detect TNF by the already described immunohistochemical method using the same internal controls.

**Statistical analysis:** Data were analyzed using  $2 \times 2$  contingency tables with the Fisher's exact test.

### RESULTS

Sensitivity, specificity and cross-reactivity of the monoclonal antibody: Our monoclonal antibody reacted with a pure 17-18 kd rhTNF alpha from a second independent source in Western blot analysis. Indirect support that our antibody was recognizing TNF alpha was that in immunohistochemically positive arteries and tumors we could also detect by ELISA, whereas there was

FIGURE 1 (opposite). Immunohistochemical detection of tumor necrosis factor (TNF) with anti-rhTNF alpha monoclonal antibody using indirect peroxidase-labeled antibody technique and diaminobenzidine substrate. Immunoreactive TNF appears in brown A, necrotizing colonic carcinoma. TNF positivity is localized to the macrophages and other inflammatory cells, and also to the tumor cells (T), while the stroma is free of staining ( $\times$  500). B, negative control of the staining shown in A. Primary antibody has been absorbed with excess rhTNF alpha. Structures positive in A do not stain here (× 500). C, complete cross-section of a human anterior tibial artery with an obstructive atherosclerotic plaque. Original lumen is obliterated by atheroma (hematoxylin and eosin stain, × 50). D, immunohistochemical staining of the same artery for TNF. This lower power photomicrograph shows localization of TNF in medial smooth muscle cells (SM), and vasa vasorum (V) ( $\times$  50). E, higher magnification of an area in D. Note TNF positivity in the medial SM, in proliferating intimal smooth muscle cells (arrows) and in newly formed vessels within the plaque (arrowheads) ( $\times$  250). F, cross-sections of medial smooth muscle cells of a vaso vasorum showing membrane bound staining characteristic of medial SM ( $\times$  850). G, intimal smooth muscle (stellate) cells from an atheroma of a human coronary artery showing TNF positivity in the cytoplasm. This pattern is characteristic of proliferating intimal smooth muscle cells (> 850). H, endothelial cells lining a newly formed vessel in an atheroma in an anterior tibial artery with TNF positivity (× 850). I multiple layers of proliferating endothelial cells of a human coronary artery with an ulcerative/thrombotic occlusive plaque. Cytoplasmic staining occurred in endothelial cells lining the original lumen of coronary arteries with complicated plaques. These cells were identified as endothelial cells by factor VIII staining (imes 650). J, TNF positive macrophages in an adventitial inflammatory infiltrate around a coronary artery with an ulcerated plaque. TNF positivity was always localized to the cytoplasm of the macrophages (× 650). K, TNF positive foam cells from a necrotic area of a nonulcerated coronary artery plaque (× 850).

**TABLE II** Frequency of TNF Positivity in Three Different Cell Types as a Function of Three Histologic Categories

	Atherosclerotic	Intimal Thickening	Normal
Smooth muscle cells	43/65	3/11	0/6
Macrophages	31/65	0/11	0/6
Endothelial cells	12/65	2/11	0/6
Tissue section	57/65	3/11	0/6

The differences between normal and diseased vessels were statistically significant. In the atherosclerotic category the difference in prevalence between both smooth muscle cells and macrophages versus endothelial cells was statistically significant.

no detectable TNF present in immunohistochemically negative brain tissue. T lymphocytes (as identified by T11), source of TNF beta, did not show immunohistochemical positivity for TNF alpha, suggesting that TNF beta was not a cross-reactor with our antibody.

As a positive control, we used colon cancer samples, where TNF is frequently present in high quantity. Figure 1A shows the immunohistochemical detection of TNF in a section of a colonic carcinoma. Although the positive TNF stain in macrophages was expected, some of the cancer cells were also found to stain positively. Positive staining was strictly localized to the cytoplasm of monocytes and tumor cells; stroma was free of staining. Figure 1B shows a negative control (primary antibody absorbed with excess of rhTNF) from the same tumor. In this specific colon cancer, we independently measured TNF by ELISA as 2.15 ng/mg. In 5 brain samples (negative controls), we did not find immunoreactive TNF with either immunohistochemistry or ELISA. In the sections that stained positive for TNF, the level of TNF measured by ELISA was approximately 3 times higher than the normal serum range established by the kit manufacturer.

Tumor necrosis factor positivity in normal and atherosclerotic vessels: Figure 1C is a section classified by hematoxylin and eosin as significantly atherosclerotic. This is a proliferative, occlusive atheroma. Figure 1D shows the distribution of immunohistochemical staining for TNF on the same tissue block. Intensive positive brown staining is localized in the smooth muscle cells of the media, the vasa vasorum and proliferating intimal smooth muscle cells. To confirm the presence of TNF independently, we measured TNF by ELISA in 2 atherosclerotic vessels; the levels were 1.25 and 0.70 ng/mg.

The frequency of TNF positivity in normal and atherosclerotic sections as a function of histologic classification is shown in Table II. Of the 82 sections, 6 were classified as normal, 11 as having intimal thickening (<10% luminal narrowing) and 65 as atherosclerotic. In the 6 histologic sections classified as normal there was no detectable TNF. In the 11 sections classified as intimal thickening, 5 (45%) had TNF positivity; of 65 sections classified as atherosclerotic, 57 (88%) were TNF positive in at least 1 cell type (p <0.0001). In coronary sections, those with acute endothelial disruption and thrombosis appeared to exhibit the most TNF positivity. In coronary arteries where the sections were made at different levels (i.e., including both normal areas and

complicated plaque) we observed the same pattern of increasing TNF positivity as the ulcerated plaque area was approached.

We also tried to determine if TNF positivity was a generalized vascular phenomenon. In TNF-positive samples, we examined both adjacent veins and sections of the gastrocnemius containing normal small muscular arteries. None of the sections was positive.

Cellular distribution of tumor necrosis factor: TNF positive staining was found in 3 types of cells: smooth muscle cells, endothelial cells and macrophages. Smooth muscle cells rather than macrophages were the most frequently positive. Figure 1E, a magnified portion of Figure 1D, reveals that positive smooth muscle cells were found in the media, vasa vasora and newly formed vessels. The distribution and extent of smooth muscle cell positivity varied from scattered to confluent.

Table II summarizes the frequency of TNF positivity in the 3 cell types. Smooth muscle cells were TNF positive in 43 of 65 (66%) of the sections classified as significantly atherosclerotic by hematoxylin and eosin staining, and 3 of 11 (27%) segments classified as intimal thickening (p <0.001). TNF positive macrophages were found in 31 of 65 (43%) of atherosclerotic lesions and in none of the segments classified as normal or minimally atherosclerotic (p <0.00001). Endothelial cell positivity was least frequently encountered. Twelve of 65 (18%) of the atherosclerotic sections and 2 of 11 (18%) of arteries with intimal thickening had endothelial cells with TNF positivity. There was no TNF positivity in normal arteries. There was no apparent difference in TNF positivity related to anatomic site or method of procurement, independent of histologic classification.

Pattern of localization within cells: Although subject to potential redistribution during fixation, the cellular localization of positive staining gives some insight as to whether a cell is a source or a target of the cytokine. A target cell has surface-bound cytokine; a source has the substance in the cytoplasm. Figure 1F shows a crosssection in which TNF positivity is confined to the cell membrane of medial smooth muscle cells. Figure 1G shows a section taken through a developing atheroma, in which TNF positive, phenotypically modulated smooth muscle cells (stellate cells) are localized in the intima. These cells were identified as smooth muscle cells by HHF35 staining (Figure 2). In developing atheroma, the earliest TNF positivity was found in these intimal smooth muscle cells in cytoplasmic rather than peripheral localization.

The capability of vascular smooth muscle cells to express immunoreactive TNF was demonstrated in a pilot tissue culture study where normal aortic smooth muscle cells were incubated with LDL (Figure 3).

Figure 1H shows TNF positivity of endothelial cells in a newly formed vessel. In areas of endothelial ulceration, TNF positivity was found in the cytoplasm of proliferating endothelial cells arranged in multiple layers (Figure 1I). We also examined sections for evidence of increased prevalence of thrombosis in the small vessels that were lined with TNF positive endothelial cells, but were unable to find such an association.

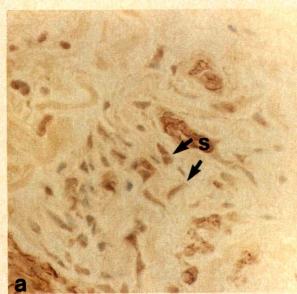
Figure 1J and K show a high power view of the TNF positive macrophages. TNF positive macrophages were found both in adventitial inflammatory infiltrates and in the atheroma as foam cells. In contrast to the surface localization of TNF in smooth muscle cells, TNF positivity was always found in the cytoplasm of the macrophages.

### DISCUSSION

The most significant finding in this study is the discovery of TNF in atherosclerotic arteries. We also report for the first time that TNF appears in both smooth muscle and endothelial cells, using the immunohistochemical technique that we developed.

To document the specificity of the TNF antibody, we performed Western blotting with rhTNF alpha, and measured TNF by ELISA on extracted fresh vascular homogenates. The tissue extract study revealed a measurable amount of TNF. For negative controls we used a standard approach. Our immunohistochemical negative controls (antibody-deleted and TNF-negative tissue) did not show any immunohistochemical staining.

Macrophages are known as the principal source of TNF. The macrophage is also a prominent cell type in



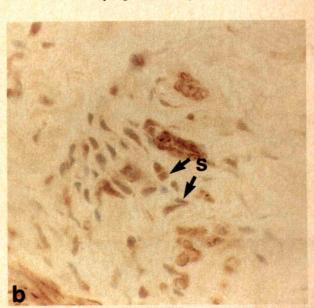
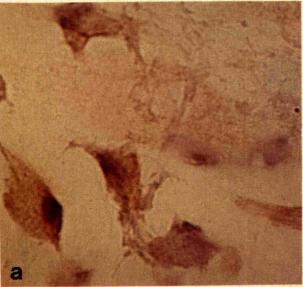


FIGURE 2. Identification of TNF positive intimal cells as smooth muscle cells by HHF35, an alpha and gamma actin specific monoclonal antibody in adjacent sections. Immunohistochemical staining used indirect peroxidase-labeled antibody technique Immunoreactive TNF and actin appears in brown. Hematoxylin nuclear staining. A, group of intimal (stellate) cells (S) with cytoplasmic positivity for TNF (× 850). B, group of intimal (stellate) cells (S) in an adjacent section to A stained by HHF35. The same group of cells shows cytoplasmic HHF35 positivity, supporting the smooth muscle character of these cells (X 850).



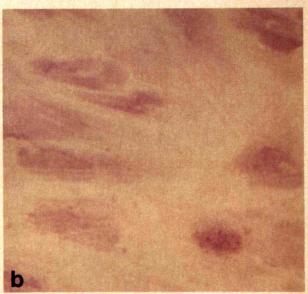


FIGURE 3. Expression of immunoreactive TNF (in brown) in primary vascular smooth muscle cell culture after incubation of cells with 100  $\mu$ g/ml LDL for 24 hours. Immunohistochemical staining for TNF and hematoxylin nuclear staining. A, culture after 24hour incubation with LDL. The cytoplasm of the cells appears in brown, supporting that immunoreactive TNF is expressed in these cells ( $\times$  1,000). B, culture without LDL incubation are TNF negative (lack of brown color in cytoplasm) ( $\times$  1,000).

the necrotic core of atheroma. 18,19 There are at least 2 stimuli that, in theory, might induce a tissue macrophage in an atheroma to produce TNF. These stimuli, lipid ingestion and decreased oxygen tension, both cause cultured monocytes to produce TNF (P. Barath, unpublished data). The possibility that postmortem anoxia stimulated TNF production by macrophages seems unlikely for 2 reasons. First, there was no postmortem TNF positivity in the macrophages of normal arteries. Second, fresh tissue obtained at surgery was strongly positive for immunoreactive TNF. The cytoplasmic staining suggests that in atheroma the macrophage is a source of TNF.

In contrast to the macrophage data, the finding of TNF positivity in smooth muscle and endothelial cells was not anticipated. Although a number of mesenchymal and epithelial cell lines produce TNF. 20-22 TNF positivity has not previously been detected in situ vascular smooth muscle or endothelial cells. The peripheral staining pattern may represent receptor-ligand interaction, endocytosis or extracellular matrix binding. Our method of preparation and the resolution of light microscopy do not allow us to separate these possibilities, but it may represent membrane-associated TNF recently described in monocytes.<sup>23</sup> The localization of TNF in the cytoplasm of some smooth muscle cells suggests that these cells also may be capable of producing TNF. Recently, capability of smooth muscle cells to express the TNF gene has been demonstrated in cultures by Northern analysis<sup>24</sup> and in human vascular tissue by in situ hybridization (P. Barath, submitted for publication). In a pilot study we demonstrated that LDL uptake induces the expression of immunoreactive TNF in vascular smooth muscle cell culture. This mechanism may be operative in natural induction of TNF expression during atheroma evolution.

Endothelial cell TNF positivity at the site of new vessel formation is potentially important, because neovascularization is a prominent part of atheroma evolution, and TNF is an unusually potent stimulus to new vessel formation.

Potential relevance to clinical coronary disease: We have demonstrated a high occurrence of endothelial ulceration and thrombus formation in coronary arteries of unstable angina patients. 25,26

The demonstration of TNF in human atheroma, combined with its known biologic effects in other tissues, suggests some speculation as to its biologic role. TNF is a powerful angiogenic factor, even in low concentration,3 and is capable of causing necrosis within 24 to 48 hours in cells that are sensitive to its actions.<sup>2</sup> Both new vessel formation and central necrosis are known to precede atheromatous endothelial disruption. 11,12 Thus, while our data do not establish a causeeffect relation, the presence of TNF and its previously established cellular actions suggest that it could be involved in the evolution of atheroma.

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### **Quantitative Analysis of Amounts of Coronary Arterial Narrowing in Cocaine Addicts**

Frederick A. Dressler, MD, Sonya Malekzadeh, BA, and William C. Roberts, MD

From January 1979 to February 1989, 22 cocaine addicts were studied at necropsy. The 22 patients were divided into 2 groups: death associated with increased cocaine levels at necropsy (13 patients, aged 23 to 45 years [mean 32], and mean total blood cocaine level, 0.36 mg/dl) and noncocainerelated death (9 patients, aged 15 to 50 years [mean 32]). Of the 22 patients, 17 were men and 5 were women; 19 were black and 3 were white. Gross examination in the 22 patients disclosed that 8 patients (36%) had 1 or more of the 4 major (left main, left anterior descending, left circumflex, and right) coronary arteries narrowed at some point >75% in cross-sectional area by atherosclerotic plaque. In 17 cases, the 4 major epicardial coronary arteries were divided into 805 five-mm long segments and a histologic section was prepared from each segment: of the 12 patients with a cocaine-related death, 41 (8%) of 544 five-mm coronary segments were narrowed 76 to 100% and 106 segments (19%) were narrowed 51 to 75% in cross-sectional area by plaque. Of the 5 cocaine addicts who did not die from cocaine overdose, 8 (3%) of 261 five-mm coronary segments were narrowed 76 to 100% and 19 segments (7%) were narrowed 51 to 75% in cross-sectional area by plaque. The frequency of coronary artery disease was greater in patients dying with cocaine in their blood at necropsy compared to those whose death was not cocaine related. Also the frequency of severe coronary arterial narrowing is considerably greater than expected for the entire group of patients whose mean age was only 32 years. Thus, either of 2 possibilities, alone or in combination, may explain our findings: coronary atherosclerosis is accelerated by cocaine addiction for reasons as yet undetermined, or cocaine provides a fatal stress in patients with premature coronary atherosclerosis from other causes.

(Am J Cardiol 1990;65:303-308)

ince the outbreak of epidemic drug abuse in the USA, several reports have described coronary (myocardial infarction, angina pectoris, arrhythmias and coronary arterial narrowing by angiogram) and noncoronary heart conditions (cardiomyopathy, myocarditis, contraction band necrosis and primary myocardial toxicity) in cocaine addicts.1-19 Although several studies have mentioned coronary arterial findings at necropsy in cocaine addicts, no reports have provided results of detailed examination of these arteries at necropsy. The present report provides such findings.

### **METHODS**

During the last 10 years we have studied at necropsy 22 known cocaine addicts, who also were known not to use opiates. The autopsies were performed at 5 different institutions and subsequently the heart and often portions of other organs were submitted for examination to the Pathology Branch, National Heart, Lung, and Blood Institute. Each heart was examined initially by one of us (WCR) and in 18 cases the heart was reexamined by 2 of us (FAD, SM). Of the 18 hearts that were reexamined, the coronary arteries were intact in 17, and in each of these 17 the 4 major (right, left main, left anterior descending, left circumflex) epicardial coronary arteries were studied in detail. Also examined in 20 patients were 1 to 11 histologic sections (mean 5) of left ventricular wall. These sections extended from endocardium to epicardium and measured at least 2 cm in lon-

The ages of the 22 patients ranged from 15 to 50 years (mean 32); 17 (77%) were men and 5 (23%) were women; 19 (86%) were black and 3 (14%) were white. The form and route of cocaine use was known in 9 patients: powder inhaled through the nose in 4; powder inhaled through the nose and slurry injected into a systemic vein in 2; smoke inhaled through the mouth in 2; smoke inhaled through the mouth and powder eaten in 1. Systemic hypertension was believed to be present in 5 patients (23%) and 3 (14%) were known to use alcohol

to excess.

Of the 22 patients, the only symptom of cardiac dysfunction or myocardial ischemia before death was congestive heart failure in 4 (nos. 5, 11, 14 and 22, Table I). The onset of congestive heart failure in each was within 2 months of death; each had hearts weighing >400 g, and each had massively dilated ventricular cavities. A single coronary artery was narrowed >75% in cross-sectional area by plaque at some point in 2 of these 4 patients (nos. 11 and 22, Table I). Patient 14 had a large, posterior wall, transmural left ventricular scar without significant coronary narrowing, and he was awaiting cardiac transplantation when he died.

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TABLEICH	TABLE I Clinical and Morphologic Cardiac Findings in 22 Cocaine Addicts	Cardiac Fi	indings in 22	Cocain	ne Add	licts													
Age (vrs)		die of	Total Blood			Narr >75%	Narrowing >75% in CSA	SA	No.	No. of 5-n	nm Coror	No. of 5-mm Coronary Segments	nents						
Pt Race,		Outside			MH	by Plaque	adne		Soronary Coronary	Narrowed	Narrowed in CSA by Plaque	y Plaque				No.		^	
No. Sex	Modes of Death	Hospital	(mg/dl)	_	(g)	LM LAD		LC R S	Segments	0-25%	26-50%		51-75% 76-95%	96-100%	Score	Sections LV + VS	(0 to 3+)	Z	FP PP
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Group II: Death	Group II: Death not due to cocaine			Property of the second								3100							
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	Infective endocarditis	10	0			0	00	6 0				0	0	0	1.00	7	+++		(A) +
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* avcessive alcohol come	hal consumption also during the	2		(181) (481) 0	7 (19	-	-	97 7	261[100]	215[82] 19	19[7] 1	19[7]	8[3]	0	(1.31) 25(4)	5(4)	2	4	-

\*excessive alcohol consumption also during the several hours before death; 'iidopathic dialed cardiomyopathy; 'thrombus also present superimposed on plaque; 'sorganized thrombus, left ventricular cavity; 'dystrophic calcification; 'i in hospital last 9 days of life, \*\*in hospital cocaine measurements at time of death; 'Hetiology unknown; '8 although no cocaine was detected in blood, the urine-free cocaine was 0.0029 mg, 0d. and the urine cocaine metabolite was 0.042 mg, 0d. and the urine cocaine metabolite was 0.042 mg, 0d. and the urine cocaine metabolite was 0.042 mg, 0d. and the urine cocaine metabolite was 0.042 mg, 0d. and the urine cocaine metabolite was 0.042 mg, 0d. and the urine cocaine metabolite was 0.042 mg, 0d. and the urine cocaine metabolite was 0.042 mg, 0d. and the urine cocaine metabolite was 0.042 mg, 0d. and the urine cocaine metabolite was 0.042 mg, 0d. and the urine cocaine metabolite was 0.042 mg, 0d. and the urine cocaine metabolite was 0.042 mg, 0d. and 0d. a

The 22 patients were divided into 2 groups. The 13 group I patients all died suddenly outside the hospital and all had toxic levels of cocaine in their blood. Cocaine overdose was the mode of death in 11 of these 13 patients. Of the other 2 patients, 1 died of an aortic dissection and he had the highest blood cocaine levels of any of the 13 patients. It is believed that his cocaine intake raised the systemic blood pressure acutely and

that the resulting hypertension led to the aortic dissection. This patient has been reported elsewhere.<sup>21</sup> The other patient, a middle-aged woman (no. 13, Table I), whose identity was never known, died of a gunshot wound but had toxic levels of cocaine in her blood at necropsy.

The 9 group II patients were known to be habitual users of cocaine. In contrast to the group I patients,

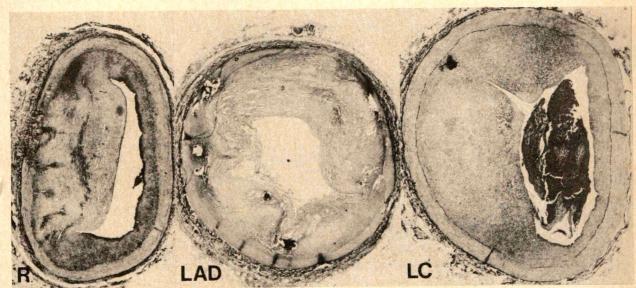


FIGURE 1. (Patient 3, Table I). Right (R), left anterior descending (LAD) and left circumflex (LC) coronary arteries at sites of maximal narrowing in a 25-year-old man (DCMEO #79-01-107) who suddenly developed chest pain shortly after a meal and died. The blood cocaine concentration at necropsy was 0.60 mg/dl. Considerable amounts of atherosclerotic plaque were present in 21 of the 48 five-mm segments of coronary artery. A thrombus also is present in the residual lumen of the left circumflex coronary artery. Movat stains,  $\times$  25 (R and LAD),  $\times$  40 (LC).

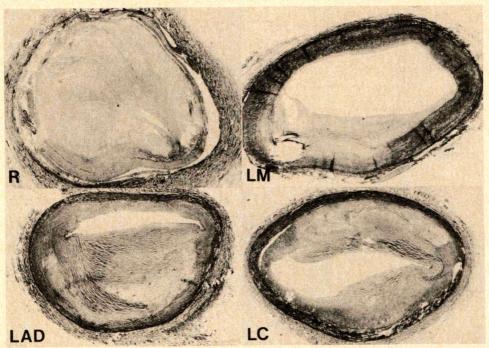


FIGURE 2. (Patient 7, Table I). Right (R), left main (LM), left anterior descending (LAD) and left circumflex (LC) coronary arteries at sites of maximal narrowing in a 32-year-old woman (DCMEO #88-04-450) who developed abdominal pain shortly after eating a sandwich and smoking cocaine. She died 2 hours later. The lumens of the right and left anterior descending coronary arteries are considerably narrowed by atherosclerotic plaque. Movat stains,  $\times$  32 (R, LAD and LC)  $\times$  40 (LM).

however, 6 of these 9 patients died in the hospital; 4 of them from 9 to 86 days after admission, and, therefore, cocaine would not have been expected in the blood; the other 2 patients died 10 and 24 hours, respectively, after admission and a toxicology screen was not performed in 1 and was negative in the other. The remaining 3 patients died suddenly outside the hospital: none had cocaine in the blood, but 1, who died from esophageal bleeding related to hepatic cirrhosis, had cocaine in the urine. Death in 1 patient was attributed to coronary artery disease, and the cause of the sudden death in the other patient was not determined.

#### **RESULTS**

In 8 of the 22 patients, 1 or more of the 4 major epicardial coronary arteries, by gross examination, was narrowed at some point >75% in cross-sectional area by atherosclerotic plaque: in 6 men aged 25 to 45 years (mean 34), and in 2 women, aged 32 and 50 (mean 41) (Figures 1 through 4). Of the 32 major epicardial coronary arteries in these 8 patients, 14 (44%) were so narrowed, a mean of 1.8/patient.

In 17 of the 22 cases, the 4 major epicardial coronary arteries were removed from the heart, cut into 5mm segments, decalcified, processed in alcohols and xylene, sectioned 6 \( \mu \) thick, stained by the Movat method and examined. Of the 805 five-mm coronary artery segments examined, 4 (<1%) were narrowed 96 to 100% in cross-sectional area by plaque; 45 (6%) were narrowed 76 to 95%; 125 (16%), 51 to 75%; 91 (11%), 26 to 50%; and 540 segments (67%) were narrowed 0 to 25%. A great variation in percents of 5-mm coronary segments severely narrowed occurred among the 17 patients (Table I).

The group I patients had more coronary arterial narrowing than did the group II patients. Six of the 13 group I patients and 2 of the 9 group II patients had 1 or more major coronary artery severely (>75% in cross-

sectional area) narrowed by atherosclerotic plaque. Forty-one (8%) of the 544 five-mm segments of major coronary artery in the group I patients and 8 (3%) of the 261 five-mm segments in the group II patients were narrowed severely by plaque. The average amount of narrowing of each 5-mm coronary segment (determined by mean score [Table I]) also was greater in the group I compared to the group II patients.

Calcific deposits were present in atherosclerotic plaques in 1 or more of the 4 major epicardial coronary arteries in 5 of the 17 patients examined histologically. Of the 805 five-mm coronary segments examined 19 (2%) had calcium. Multiluminal channels were present within atherosclerotic plaques in only 1 (<1%) of the 805 five-mm segments. Intraluminal thrombus was observed in a coronary artery superimposed on atheroscle-

rotic plaque in 1 patient.

Of the 22 patients, 7 (32%) had 1 or more foci of left ventricular wall necrosis. The foci of necrosis were visible on gross examination of the heart in 2 cases (nos. 15 and 22, Table I): in 1, the necrosis was limited to the inner half of the left ventricular wall (subendocardium), and in 1, the necrosis involved all of the inner half and portions of the outer half of the left ventricular wall (transmural). In the other 5 patients, the foci of necrosis were visible only on examination of the histologic sections of left ventricular wall. Only 2 of the 7 patients with left ventricular necrosis had severe narrowing of 1 or more major epicardial coronary artery.

### DISCUSSION

Our findings indicate that a large percent of young cocaine addicts have significant coronary artery disease at necropsy. Of the 22 cocaine addicts studied, 8 (36%) had severe (>75% cross-sectional area) narrowing of 1 or more of the epicardial coronary arteries by atherosclerotic plaque, a percent much higher than expected in a group of persons whose mean age is only 32 years.

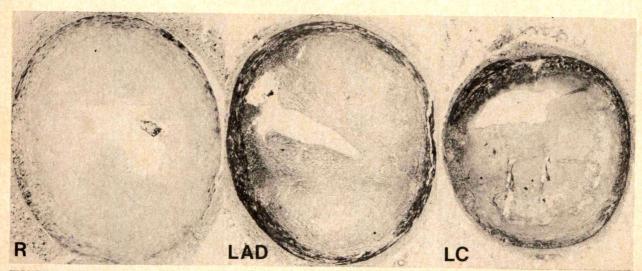


FIGURE 3. (Patient 12, Table I). Right (R), left anterior descending (LAD) and left circumflex (LC) coronary arteries at sites of maximal narrowing in a 45-year-old man (DCMEO #85-03-195) who suddenly collapsed and died after smoking "free-base" cocaine off and on for several hours. He died of an acute aortic dissection with through-and-through aortic rupture. At necropsy, however, the R, LAD and LC coronary arteries were each narrowed >75% in cross-sectional area of atherosclerotic plaque. Movat stains,  $\times$  32 (R and LC) and  $\times$  40 (LAD).

One (no. 3) of the 8 patients had an occluding thrombus superimposed on atherosclerotic plaque. Only 1 of 8 patients had a grossly visible acute myocardial infarct. (Of the other 14 patients without significant coronary artery disease, 1 [no. 15] had a grossly visible acute myocardial infarct, and 1 [no. 14] had a large healed myocardial infarct.)

At least 5 other reports have described young cocaine addicts at necropsy with "narrowing" in 1 or more epicardial coronary artery by atherosclerotic plaque with or without superimposed thrombus. Simpson and Edwards<sup>22</sup> described a 21-year-old male cocaine addict who died suddenly, and necropsy disclosed "chronic coronary obstruction ... the result of a nonatherosclerotic intimal proliferation of smooth-muscle cells, with or without the deposition of collagen and elastin." The lumen of the left main was narrowed 65%, the left anterior descending 95%, the right 95%, and the left circumflex coronary artery, apparently up to 50% in cross-sectional area. Platelet thrombus also was present in 1 or more major coronary arteries. Isner et al23 described a 37-year-old male addict who was found dead in bed and necropsy disclosed 90% cross-sectional narrowing by plaque of the left anterior descending coronary artery with superimposed obstructing thrombus, and up to 50% narrowing of the right coronary artery. The lumen of the left circumflex was narrowed up to 25% in crosssectional area. Mittleman and Wetli20 reported 24 cocaine addicts studied at necropsy and all had died suddenly. Death in 15 (aged 29 to 71 years [mean 47]) of the 24 patients was attributed to coronary atherosclerosis with ≥70% stenosis in 1 or more of the coronary arteries. This degree of luminal narrowing involved only 1 coronary artery in 8 patients and >1 in 7 patients.

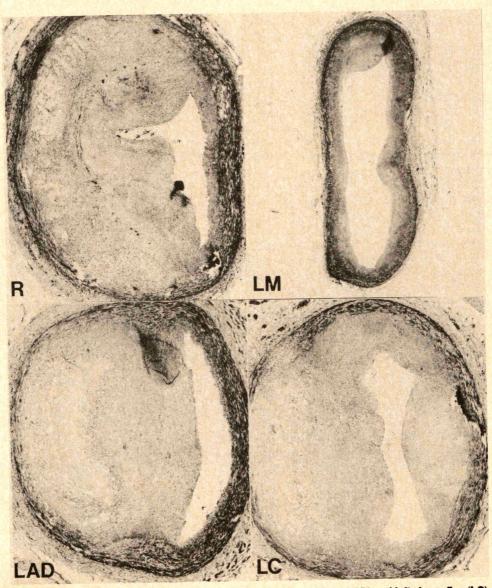


FIGURE 4. (Patient 18, Table I). Right (R), left main (LM), left anterior descending (LAD) and left circumflex (LC) coronary arteries at sites of maximal narrowing in a 30-year-old man (WCH #A85-28) who died suddenly at work while using a hydraulic lift. He had exertional chest pains periodically during the previous 1 year. Three of the 4 major coronary arteries contained considerable quantities of atherosclerotic plaque. Movat stains,  $\times$  32 (R),  $\times$  15 (LM),  $\times$  50 (LAD) and  $\times$  40 (LC).

Two patients had hemorrhage into an arteriosclerotic plaque, and 3 cases had complete thrombotic occlusion of the residual lumen. Virmani et al24 described 2 cocaine addicts with "severe coronary atherosclerosis," and another, a 23-year-old woman, who had an occlusive platelet thrombus in the left anterior descending coronary artery superimposed on a plaque that had narrowed the lumen about 40% in cross-sectional area. Finally, Stenberg et al25 described a 38-year-old male cocaine addict who died about 13 hours after onset of acute myocardial infarction. Necropsy disclosed occluding platelet thrombi in both the left anterior descending and right coronary arteries superimposed on plaque that had narrowed the lumen by 70 and 50%, respectively.

Our study is the first to describe in cocaine addicts the degree of cross-sectional area narrowing by atherosclerotic plaque in each 5-mm long segment of each of the 4 major epicardial coronary arteries. Of the 544 five-mm segments in the 12 patients who had documented toxic cocaine levels in their blood at necropsy (group I), 41 (8%) were narrowed >75% in cross-sectional by plaque alone, and 106 segments (19%) were narrowed 51 to 75% in cross-sectional area by plaque. Of the 261 five-mm segments in the 5 patients (group II) who did not have cocaine in their blood at necropsy but who were known to be habitual cocaine addicts, 8 segments (3%) were severely (>75% cross-sectional area) narrowed. Thus, it is apparent that severe coronary artery narrowing was strongly associated with death due to cocaine overdose in our patients.

The amount of severe coronary narrowing in our 2 groups of patients was higher than that expected for groups of persons whose average age is only 32 years. Of 40 patients whose epicardial coronary arteries were studied in similar fashion, who died mainly of leukemia, who never had evidence of cardiovascular disease, and whose average age was 52 years, only 3% of their 5-mm segments of the 4 major coronary arteries were narrowed >75% in cross-sectional area by plaque, and only 22% were narrowed 51 to 75% in cross-sectional area, and this group of "control subjects" was 20 years older on the average than were the cocaine addicts in the present study.26

In summary, this study suggests that cocaine addicts studied at necropsy have an increased amount of atherosclerotic plaque in their major epicardial coronary arteries. One explanation for the high frequency of premature coronary artery narrowing is that chronic cocaine use, by mechanisms not yet understood, accelerates coronary atherosclerosis. Another view is that of the large number of people, mostly young adults, who use cocaine, a small number have premature coronary atherosclerosis due to other causes. Cocaine may provide a fatal stress for this minority. Our study, like pre-

vious ones, focused on cocaine addicts who came to medical attention or died, and thus probably overestimates the frequency of coronary artery disease among all cocaine users.

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WHETHER ISCHEMIA STRIKES WITH PAINFUL VIOLENCE...

OR TOTAL SILENCE.

TENORMIN reduces more than just <u>painful</u> myocardial ischemia. It reduces <u>painless</u> ischemia as well. Alone or in combination regimens, it lowers the total ischemic burden\* and reduces the need for PRN nitroglycerin.<sup>1-3</sup>

\*The sum of painful and painless episodes.

In Angina

TENORMIN (atenolol)

PROTECTS THE HEART.



See adjacent page for brief summary of prescribing information.



A beta<sub>1</sub>-selective (cardioselective) blocking agent.

A beta,-selective (cardioselective) blocking agent.

DESCRIPTION: TENORMIN (atenolo), a synthetic, beta;-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy,3'-(1-methylethyl) amino] propoxy]. Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/mL at 37°C, and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCI (300 mg/mL at 25°C) and less soluble in colloroform (3 mg/mL at 25°C)

TENORMIN is available as 50 mg and 100 mg tablets for oral administration. Inactive ingredients: magnesium stearate, microcrystalline cellulose, povidone, sodium starch plycolate.

glycolate.

INDICATIONS AND USAGE: Hypertension: TENORMIN is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly

Angina Pectoris Due to Coronary Atherosclerosis: TENORMIN is indicated for the long-term

management of patients with angina pectoris.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. (See WARNINGS)

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients we have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administent cautiously. Both digitalis and atenolos Jose AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a perind of time can in some cases, lead to cardio cluby. At the first is:

beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues despite adequate digitali-zation and diuresis, TENORMIN should be withdrawn. (See Dosage and Administration.)

ation and diuresis, IENORMIN should be withdrawn. (See Dosage and Administration.)

Cessation of Therapy With TENORMIN: Patients with coronary artery disease, who are being treated with TENORMIN, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with other beta blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. To date, there has been no report of myocardial infarction or severe angina upon withdrawal of TENORMIN, probably due to its long plasma half-life. Because of the problems encountered with other beta blockers, when discontinuation of TENORMIN is planned the patients should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that TENORMIN be promptly reinstituted, at least temporarily. (See Dosage and Administration.)

Pronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SUCULIA.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD. IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta<sub>1</sub> selectivity, how TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta<sub>1</sub> selectivity is absolute, the lowest possible dose of TENORMIN should be used with therapy initiated at 50 mg, and a beta<sub>2</sub>-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If freatment is continued, care should be taken when using anesthetic agents which depress the myocardium such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg. dobutamine or isoproterenol with caution—see section on Overdosage). Manifestations of excessive vagal tone (eg. profound bradycardia, hypotension) may be corrected with atropine (1-2 mg IV).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as disziness and sweating may not be significantly affected.

TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers. does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg. tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely. (See Dosage and Administration.)

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function. (See Dosage and Administration.)

Drug Interactions: Catecholamine-depleting drugs (eg. reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension.

Should

concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose), and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human dose. Although similar effects were not seen in abbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 125 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mathers 4 tenglol is avgreted in human brass trility to action of the second of t

otential risk to the fetus.

Nursing Mothers: Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared the concentration in plasma. Caution should be exercised when TENORMIN is administered to a

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (US studies) or elicited, e.g. by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN (atenolo) and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship to TENORMIN is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the US studies (volunteered side effects) and then from both US and foreign studies (volunteered and elicited side effects).

icited side effects):
US STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), colo exterimino (2%-1%), leg pain (0%-0.5%), colo exterimino (2%-1%), leg pain (0%-0.5%), colo exterimino (2%-0.5%), leghtheadedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0.6%), depression (0.6%-0.5%), creaming (0%-0.6%), GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%), experimental (2%-0%), nausea (4%-1%), dyspnea (0.6%-1%) RESPIRATORY (see WARNINGS). wheeziness (0%-0%), dyspnea (0.6%-1%)

RESPIRATORY (see WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%)

TOTALS US AND FOREIGN STUDIES:
CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension
(4%-5%), leg pain (3%-1%)
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), lightheadedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (26%-0.5%), depression (12%-9%), dreaming (3%-1%)
GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%)
GESPIRATORY (see WARNINGS), wheeziness (3%-3%), dyspnea (6%-4%)
MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

Inerapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of

TENORMIN

HEMATOLOGIC. Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

ALLERGIC: Fever, combined with aching and sore throat, laryngospasm, and respiratory distress:
CENTRAL NERVOUS SYSTEM: Reversible mental depression progressing to catatonia, visual
disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time
and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased
performance on neuropsychometrics.

distributions, hallucinations, an acute reversione syndrome characterized by disorhellation of the and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

GASTROINTESTINAL: Mesenteric arterial thrombosis, ischemic collitis. OTHER. Reversible alopecia, Peyronie's disease, erythematous rash, Raymaud's phenomenon, MISCELLANEOUS. The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information of merregency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted.

BRADYCARDIA: Atropine or another anticholinergic drug.

HEART BLOCK (SECOND OR THIRD DEGREE). Isoproterenol or transvenous cardiac pacemaker. CONGESTIVE HEART FALURE. Conventional therapy.

HYPOTENSION (DEPENDING ON ASSOCIATED FACTORS): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

BRONCHOOSPASM: Aminophylline: isoproterenol, or atropine.

DOSAGE AND ADMINISTRATION: Hypertension: The initial dose of TENORMIN is 50 mg given as

DOSAGE AND ADMINISTRATION: Hypertension: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within 1 to 2 weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Anglina Pectoris: The initial dose of TENORMIN is 50 mg given as one tablet a day. If an optimal response is not achieved within 1 week, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Some patients may require a dosage of 200 mg once a day for optimal effect. Twenty-four-hour control with once-daily dosing is achieved by giving doses larger than necessary to achieve an immediate maximum effect. The maximum early effect on exercise tolerance occurs with doses of 50 to 100 mg. but at these doses the effect at 24 hours is attenuated, averaging about 50% to 75% of that observed with once-a-day oral doses of 200 mg.

Patients with Renal Impairment: Since TENORMIN is exoreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 mL/min/1.73 m<sup>2</sup>); therefore, the following maximum dosages are recommended for patients with renal impairment.

Maximum Dosage 15-35 16-27 50 mg daily 50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

Cessation of Therapy: If withdrawal of TENDRMIN therapy is planned, it should be achieved gradually over a period of about 2 weeks. Patients should be carefully observed and advised to limit physical achieved by a property of the propert

gradually over a period of about a weeks, in alternal and the control of the physical activity to a minimum.

HOW SUPPLIED: Tablets of 50 mg atenolol, NDC 0310-0105 (round, flat, uncoated white tablets identified with ICI debossed on one side and 105 debossed on the other side, bisected) are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Debet of 10 mg atenolol, NDC 0310-010 (round, flat, uncoated white tablets identified with ICI about 50 idea and 101 debossed on the other side) are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture.

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### Determinants of Hospital Charges for Coronary Artery Bypass Surgery: The Economic Consequences of Postoperative Complications

George J. Taylor, MD, Frank L. Mikell, MD, H. Weston Moses, MD, James T. Dove, MD, Richard E. Katholi, MD, Shezad A. Malik, MD, Stephen J. Markwell, MA, Cynthia Korsmeyer, RN, BS, Joel A. Schneider, MD, and Harry A. Wellons, MD

This is a prospective study of 500 consecutive patients having coronary artery bypass surgery; mean hospital charge from time of surgery to discharge was  $$11,900 \pm 12,700$ . Multiple regression analysis was performed using preoperative variables and postoperative complications. No preoperative clinical feature was a significant predictor of higher average charge. Sternal wound infection (p = 0.0001), respiratory failure (p = 0.0001) and left ventricular failure (p = 0.017) were associated with higher average hospital charge. The absence of any complication predicted a lower average charge, and postoperative death (4.4  $\pm$  4.5 days after surgery) was also associated with lower average charge. A cost equation was developed: hospital charge equalled \$11,217 + \$41,559 for sternal wound infection, + \$28,756 for respiratory failure, + \$5,186 for left ventricular failure, - \$1,798 for no complication and - \$6,019 for death. Recognition of the influence of complications on charges suggests that low average charges can only be achieved by surgical programs with a low complication rate.

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oronary bypass graft surgery consumes more health care resources than any other single treatment. Third party payors are urging programs to reduce costs and discount services. Like others, we have worked to cut costs, but are concerned that some cost-cutting measures may adversely affect our quality of care. The present study developed from efforts to assess complications and cost efficiency of our coronary bypass surgery program. We found it impossible to evaluate clinical features and hospital charges retrospectively, as face sheet analysis was too often inaccurate. Thus we prospectively examined hospital charges and related them to clinical variables for 500 consecutive patients having coronary bypass surgery between March and November 1985.

### **METHODS**

During this 9-month period, 591 coronary artery bypass operations were performed at St. John's Hospital. This study includes the 500 consecutive patients having bypass surgery performed by our surgical team (JAS and HAW). At the time of hospital discharge, the total hospital charge for care beginning on the day of surgery was recorded for each of the 500 patients, and a clinical database was completed. No patient was excluded because of unstable angina pectoris, recent thrombolytic therapy for myocardial infarction, failed percutaneous transluminal coronary angioplasty, advanced age, other concomitant surgical procedure (heart valve surgery, carotid endarterectomy, left ventricular aneurysmectomy) or any other clinical condition. The 500 operations were performed using standard techniques without surgical trainees. Moderate systemic hypothermia (24°C) was used with topical cooling. Cold blood cardioplegia was administered into the aortic root after aortic crossclamping and directly into each reverse saphenous vein graft after the distal anastomosis was completed. Internal mammary artery grafts (right and left) were routinely used. Patients were managed postoperatively by the attending cardiologist and surgeon. Pulmonary artery pressure was not routinely monitored postoperatively. Patients generally remained in the intensive care unit for 36 to 48 hours after surgery. Those with new Q waves after surgery had a radionuclide angiogram before discharge.4 All patients had phase I cardiac rehabilitation. Preoperative left ventricular ejection fraction was determined using computer analysis of the left ven-

From the Prairie Cardiovascular Center and the Southern Illinois School of Medicine, Springfield, Illinois. This study was supported in part by the Prairie Education and Research Cooperative, Springfield, Illinois. Manuscript received September 20, 1989, and accepted September 27.

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TABLE I Preoperative Clinical Characteristics and Average Hospital Charge

	No.	%	ICU Days	Hospital Days	Hospital Charge × \$1000
All pts	500	NO SERVICE SER	2.9 ± 5.5	10.0 ± 11.5	11.9 ± 12.7
Age ≥65 years	191	38	$2.7 \pm 3.7$	$10.5 \pm 6.7$	12.0 ± 6.3
Women	113	23	$3.1 \pm 4.9$	$11.8 \pm 15.5$	$12.7 \pm 11.1$
Women ≥65 years	57	11	$3.4 \pm 6.5$	$11.9 \pm 10.5$	$13.3 \pm 10.3$
Diabetes	90	18	$2.7 \pm 3.7$	12.8 ± 23.2	14.6 ± 25.0
Hypertension	250	50	$3.0 \pm 4.7$	$10.7 \pm 11.9$	12.3 ± 11.0
Cigarette smoking*	144	29	$3.2 \pm 5.9$	$9.9 \pm 9.8$	$12.3 \pm 12.3$
Obstructive lung disease	45	9	$2.9 \pm 1.5$	$10.4 \pm 6.0$	12.3 ± 4.4
Prior stroke or TIA	16	3	$3.8 \pm 4.1$	$21.4 \pm 35.3$	18.8 ± 21.8
Obesity†	96	19	$3.0 \pm 5.3$	11.9 ± 16.8	$12.5 \pm 11.9$
PVD	19	4	$5.2 \pm 11.2$	$12.7 \pm 17.0$	$15.7 \pm 17.0$
Cardiac history				12.0 2 17.0	15.7 ± 17.0
MI	279	55.8	$3.3 \pm 7.3$	$10.8 \pm 15.0$	12.8 ± 16.8¶
Thrombolysis for AMI	71	14	$2.4 \pm 1.2$	$8.7 \pm 2.8$	10.3 ± 2.3
Unstable angina‡	87	17	$2.5 \pm 1.2$	9.2 ± 3.6	11.3 ± 3.1
Second bypass	12	2	$2.0 \pm 0.9$	$7.0 \pm 3.5$	10.6 ± 2.6
Valve replacement	23	5	$3.0 \pm 1.6$	11.0 ± 6.0	14.6 ± 4.0°
Heart failure§	12	2	$2.7 \pm 1.4$	10.8 ± 6.2	$13.5 \pm 4.2$
Failed PTCA	27	5	2.3 ± 1.0	7.9 ± 2.2	11.1 ± 3.1
ngiographic findings				7.5 1 2.2	11.1 ± 3.1
Left main CAD	39	8	4.1 ± 8.2	12.5 ± 13.2	15.3 ± 19.7
1-vessel CAD	91	18	$2.3 \pm 0.8$	$8.7 \pm 4.0$	10.4 ± 3.0
2-vessel CAD	175	35	$2.9 \pm 4.0$	$10.0 \pm 12.5$	11.6 ± 9.2
3-vessel CAD	180	36	$2.8 \pm 4.0$	$9.5 \pm 6.8$	$11.0 \pm 9.2$ $11.7 \pm 9.6$
LVEF <40%	38	8	$3.0 \pm 1.6$	9.7 ± 5.1	11.7 ± 9.6 11.8 ± 4.5

<sup>\* &</sup>gt;40 pack years; † >40 pounds over ideal weight; † angina pectoris requiring intravenous nitroglycerin treatment at the time of surgery; § requiring drug therapy; † stenosis ≥70% luminal diameter.

p <0.05 (Student *t* test).

CAD = coronary artery disease; ICU = intensive care unit; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; PVD = peripheral vascular disease; TIA = transient ischemic attack.

TABLE II Postoperative Complications and Average Hospital Charge for 500 Patients

	No.	%	ICU Days	Days	Hospital Charge × \$1000
No complication	157	31.4	2.1 ± 0.5	7.8 ± 1.6	9.4 ± 1.2 **
Respiratory failure*	14	2.8	$18.9 \pm 29$	43.2 ± 57.6	49.5 ± 66.6 **
Reoperation for bleeding	27	5.4	$3.1 \pm 1.9$	$10.5 \pm 3.9$	$14.1 \pm 4.4$
Sternal infection <sup>†</sup>	2	0.4	$35.5 \pm 24.7$	$120.0 \pm 45.3$	115.6 ± 24.4**
Wound dehiscence	3	0.6	$3.7 \pm 1.5$	18.3 ± 3.2	20.6 ± 2.0
Pulmonary embolism	6	1.2	$4.2 \pm 1.6$	$16.7 \pm 10.1$	17.3 ± 4.5
Myocardial infarction <sup>‡</sup>	15	3	$3.1 \pm 1.4$	$8.7 \pm 4.6$	13.1 ± 3.8
Stroke or TIA	11	2.2	$3.6 \pm 2.1$	14.1 ± 6.4	15.3 ± 5.3
LV failure§	34	6.8	$5.0 \pm 8.8$	$13.1 \pm 15.5$	18.5 ± 20.9**
Atrial fibrillation¶	97	19.4	$3.6 \pm 7.1$	12.2 ± 11.6	13.9 ± 14.7
Ventricular ectopy	174	34.8	$2.7 \pm 1.8$	$10.5 \pm 11.6$	$13.3 \pm 14.7$ $12.2 \pm 7.5$
Death	16	3.2	$2.8 \pm 2.7$	$4.4 \pm 4.5$	12.9 ± 5.1**

<sup>\*</sup> Required ventilator support for >2 days; † positive wound culture requiring antibiotic therapy; † new Q waves plus new regional wall motion abnormality on radionuclide angiogram; § left ventricular failure requiring intraaortic balloon counterpulsation; † arrhythmia prompting drug therapy.

† p <0.05 (univariate analysis); \*\* p <0.05 (multivariate analysis).

tricular angiogram.7 Charges for preoperative catheterization, angioplasty, hospitalization while awaiting surgery and professional services (cardiology, anesthesiology and surgery) were not included.

The influence of each clinical variable (Tables I and II) on hospital charges was tested with univariate (Student t test) and multiple regression analysis.8

### RESULTS

Mean age of the 500 consecutive patients having surgery was 61 ± 9 years (median 62); 191 were at least 65 years old, 113 were women and 57 of the women were at least 65 years old. Coronary bypass alone was performed in 457 patients, and 43 had an addition-

al procedure including valve replacement in 23, left ventricular aneurysmectomy in 5, carotid endarterectomy in 6 and another, noncardiac surgical procedure in 10. Surgery 4 ± 4 days (range 0 to 18) after thrombolytic therapy for acute transmural myocardial infarction was performed in 71 patients, and 16 other patients had emergency surgery in a setting of chest pain after failed percutaneous transluminal coronary angioplasty. Average time in-hospital after surgery was 10 ± 11.5 days (median 8). Surgical mortality in the hospital was 16 of 500 (3.2%). Clinical outcome and complications from this series have previously been reported.3,4

The average number of bypass grafts per patient was 3.5 ± 1.4 (median 4). An internal mammary graft was

TABLE III Hospital Charges for Six Illinois Heart Surgery Programs in 1986

	St. John's Springfield	Rush Presbyterian Chicago	Loyola Maywood	Mercy Urbana	St. Francis Peoria	Illinois Masonic Chicago
CU per day	215*	699	829	285 <sup>†</sup>	888	979
Room rate	208	390	392	240	240	345
Chest x-ray	38	61	54	48	60	66
Complete blood count	16	23	15	19	20	33
Electrocardiogram	47	48	25	47	68	65
Operating room <sup>‡</sup>	4020	2595	3814	6668	6991	5475
Anesthesia‡	490	543	2365	1178	1025	411
ORG 106	15.725	29,547	33,410	49,505	32,380	60,328
JRG 100	n = 468	n = 183	n = 384	n = 29	n = 100	n = 33
DRG 107	13.779	23.728	22,489	31,481	25,079	38,765
DKG 107	n = 259	n = 320	n = 744	n = 138	n = 175	n = 64

\* Does not include a \$15/hour nursing charge and a \$34 daily telemetry charge, which brings the total charge to \$599/day.

† Does not include an hourly nursing charge or telemetry charge.

† Operating room and anesthesia charges are not fixed, but vary with duration of the operation and include charges for reoperation; the reported charge is the average for 1986. ICU = intensive care unit; DRG 106 = cardiac catheterization and bypass surgery in 1 hospitalization; DRG 107 = hospital admission for bypass surgery without cardiac theterization.

used in 476 of the 500 patients; 273 (55%) had both right and left internal mammary grafts. Ischemic time during surgery was  $47 \pm 21$  minutes (range 9 to 199, median 46). Average transfusion per patient was 2.4 ± 3.5 units of blood or packed cells. Average hospital charge in this 1985 study was \$11,900 ± \$12,700 (median \$9,970).

Table I describes the patient population and relates clinical characteristics to average hospital charge. Only a need for valve replacement and history of myocardial infarction were significant (p <0.05) univariate predictors of a higher average charge when patients with these characteristics were compared to those without. Complications of surgery are summarized in Table II, and several of these complications were univariate predictors of higher average hospital charge.

Multiple regression analysis was performed using preoperative variables (Table I), postoperative complications (Table II) and a single operative variable, ischemic time. The program allowed entry of continuous as well as categorical variables.8 No preoperative clinical feature was a significant predictor of higher average charge. Sternal wound infection (p <0.001), respiratory failure (p <0.001) and left ventricular failure requiring intraaortic balloon counterpulsation (p = 0.017) significantly predicted higher average charge. The absence of any complication predicted a lower average charge (p <0.05). Death usually occurred early after surgery (4 ± 5 days); for this reason, death also was associated with a lower average charge (p <0.05). Using these variables an equation was developed that predicted hospital charge: hospital charge = a baseline charge of \$11,217, + \$41,559 for sternal wound infection, + \$28,756 for respiratory failure, + \$5,186 for left ventricular failure, - \$1,798 for no complication and - \$6,019 for death.

#### **DISCUSSION**

The present study indicates that surgical complications, not preoperative variables, are the clinical features most likely to escalate hospital charges. Recognition of the powerful influence of complications on charges for coronary bypass surgery suggests that a low average charge can only be achieved by programs with a low complication rate. Conversely, a high complication rate would make it impossible for a program to have low charges.

A potentially important corollary of this association of complications and hospital charges is that average, total hospital charge might provide some indication of a heart surgery program's complication rate. Assessing the quality of surgical programs is difficult. Reporting complications on face sheets is subject to bias; retrospective, face sheet and chart analysis have been shown to underestimate the frequency of complications.9 Programs with low complication rates willingly analyze surgical morbidity.3,5 Programs with higher complication rates, however, may be reluctant to publish their results. On the other hand, the total hospital charge, the final amount that is billed to the patient, is impossible to manipulate. It is also a figure that is closely monitored and is public information in most states.

A potential criticism of this study is that the average hospital charge was unusually low. It happens that the Illinois Health Care Cost Containment Council monitored hospital charges for each of the coronary bypass surgery programs in Illinois in 1986, and it confirmed unusually low charges for St. John's Hospital. 10,11 The average hospital charge for bypass surgery in Illinois in 1986 was \$26,000 (averaging Diagnosis Related Group numbers 106 and 107); for St. John's Hospital the average charge was \$15,000, which is 42% less. The difference between the average charge reported in the present study (last half of 1985) and the Illinois Health Care Cost Containment Council (1986) is explained by the exclusion of all preoperative charges in our study and by the fact that our surgical team performed just 85% of the surgery at St. John's Hospital in 1985.

We see 3 possible explanations for the lower average hospital charge at St. John's Hospital. The first is lower mark-up of services. There is a well-documented difference between costs and charges, 12,13 costs may be higher in urban centers14 and the mark-up philosophy at St. John's Hospital has been conservative. Table III compares line item charges for representative surgical pro-

grams in Illinois, 10 and it indicates lower line item charges for St. John's Hospital. But even comparison of line item charges is subject to error. 13 For example, the low intensive care unit charges at Mercy and St. John's Hospitals did not include an hourly charge for nursing care and telemetry that, when included, brought the total intensive care unit charge into the range reported by other programs. The reported operating room charge (Table III) was not a uniform charge but instead was the average for that program during 1986. It was influenced by the duration of each operation and included charges for reoperation when needed. Despite this uncertainty in comparing baseline charges, St. John's Hospital appears to have somewhat lower mark-up, and this would explain some difference in average charge (but not \$11,000/case).

A second explanation for lower charges could be higher efficiency. We have adopted most of the costsaving measures emphasized by physicians who have studied this area, 15-17 although we still admit patients the night before surgery. In addition, others have shown that high volume programs use fewer ancillary services such as laboratory, x-ray and invasive monitoring. 18,19 Higher utilization of ancillary services and lower efficiency have been found in surgical training programs. 20,21

The present study of hospital charges suggests that a third contributor to low average charge is a low complication rate (Table III). Nelson and Dries<sup>22</sup> have described higher hospital charges for patients with wound infection. Ours, however, is the first study of bypass surgery to assess systematically the influence of any complication on hospital charges.

There is a growing body of evidence linking surgical volume to morbidity and mortality. 18,19,23,24 The Illinois Health Care Cost Containment Council report links surgical volume to charges. Our data relate morbidity and charges. Showstack et al23 found that low volume programs had more patients with unusually long hospitalizations, presumably due to surgical complications, and prolonged hospitalization means higher charges. However, we would emphasize that length of stay can not be substituted for analysis of hospital charges, as the cost of care for any complication involves more than just a bed charge. Some complications will be more expensive to treat. For example, 10 additional hospital days on a ventilator with respiratory failure would cost far more than 10 additional hospital days because of stroke. Charges related to a specific complication take into account not only increased length of hospitalization but also the particular expenses incurred treating that complication (Table III).

While it does not affect the analysis of data within our own program, patient selection may introduce error when comparing different surgical programs. 10,23,24 Could it be that high cost 10 or high morbidity/mortality<sup>23,24</sup> programs operate on sicker patients? This seems doubtful as programs with higher morbidity and mortality also tend to have lower volume; low volume programs are more likely to avoid difficult cases.

There were 17 programs in the Illinois Health Care Cost Containment Council study that reported <100 bypass operations in 1986; the average charge for these low volume centers was \$38,000, 46% higher than the state average and 153% higher than St. John's Hospital. 10 This finding and the results of previous studies of surgical volume and clinical outcome support regionalization of coronary artery bypass surgery into higher volume centers. 18,19,23-25 The present, uncontrolled trend of opening new, and of necessity, lower volume surgical programs must result in dispersion of cases, lower volume for all programs, higher complication rates and thus higher hospital charges.

In most economic systems, higher quality services cost more. The present data suggest that, paradoxically, higher quality coronary bypass surgery may cost less. Regardless of the explanation for lower charges, third party payors would be wise to direct patients to such programs. Our data suggest that this not only makes sense economically, but also clinically, as low hospital charges follow lower surgical morbidity.

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### Attenuation of Exercise-Induced ST Depression During Combined Isometric and Dynamic Exercise in Coronary Artery Disease

Kim Bertagnoli, MS, Peter Hanson, MD, and Ann Ward, PhD

ST-segment depression was measured during submaximal dynamic (treadmill) and combined isometric-dynamic (isodynamic) exercise at comparable rate-pressure products in 11 patients (mean age 63 years) with stable coronary artery disease who were participating in an exercise training program. Each patient completed 3 separate trials. Trial 1 (baseline) was a submaximal treadmill exercise test to determine the threshold heart rate-systolic blood pressure (rate-pressure product) for ST-segment depression (≥1.0 mm). During trials 2 and 3, patients performed (in random order) dynamic treadmill exercise and isodynamic exercise (treadmill walking 1.5 to 2.0 mph carrying 15 to 25 kg) until threshold rate-pressure product was achieved. During trial 1, each patient showed significant ST depression (mean 1.7 mm) at target rate-pressure product (mean 18,200). Subsequent dynamic exercise trials 2 and 3 showed similar mean ST depression (1.5 mm) and rate-pressure product (18,000). During isodynamic exercise trials 2 and 3, subjects showed only minimal ST depression (mean 0.4 mm) at a rate-pressure product similar to dynamic exercise (mean 18,590). Heart rates were significantly lower (-10/min) and systolic (+20 mm Hg) and diastolic (+25 mm Hg) pressure was higher during isodynamic exercise (p < 0.05). The rate-pressure product is not a valid index of ST response during isodynamic exercise in stable exercise-trained cardiac patients. Attenuation of ST depression during isodynamic exercise may be attributed to a combination of increased diastolic perfusion pressure, decreased heart rate and possibly to reductions in venous return and ventricular diastolic wall tension due to increased intrathoracic and abdominal pressure.

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yocardial oxygen demand has been shown to correlate with the product of heart rate and systolic blood pressure during dynamic exercise in normal subjects<sup>1,2</sup> and in patients with coronary artery disease.<sup>3</sup> Stable angina patients usually demonstrate this parallel relation between myocardial oxygen demand and rate-pressure product by exhibiting ischemic electrocardiographic (ECG) changes or angina at a reproducible rate-pressure product during dynamic exercise.<sup>4,5</sup>

Patients with coronary artery disease have traditionally been advised to avoid activities that require isometric muscle contraction due to the reflex increase in systolic blood pressure and corresponding rate-pressure product. However, several recent studies<sup>6-11</sup> have reported that coronary artery disease patients frequently show less ischemic ECG responses and a delayed angina threshold while performing isometric or combined isometric and dynamic (isodynamic) exercise compared to dynamic exercise alone. These studies did not compare ST depression at similar rate-pressure products during dynamic and isodynamic exercise.

The purpose of this study was to determine if ST depression is attenuated during isodynamic exercise in stable coronary artery disease patients who showed repeatable ST depression during dynamic treadmill exercise. We compared ECG responses during submaximal dynamic treadmill exercise and isodynamic (weight carrying) treadmill exercise performed at equivalent rate-pressure product values known to elicit ST depression ≥1.0 mm during dynamic exercise.

#### **METHODS**

Subject selection: Eleven male subjects (mean  $\pm$  standard deviation age  $63 \pm 7$  years) were selected from the population of regular participants in the University of Wisconsin Hospital Outpatient Cardiac Rehabilitation Center. All subjects volunteered to participate in the study and signed a consent form approved by the Committee for Human Subjects.

Five subjects had documented myocardial infarction and 2 had coronary bypass surgery without a prior myocardial infarction. The remaining 4 subjects had coronary artery disease without prior infarction. Left ventricular contractile pattern determined by cardiac catheterization was normal in 3 and mild or moderately impaired in the remaining 8 subjects.

The physical and clinical characteristics of the subjects are summarized in Table I. The mean maximal treadmill exercise capacity (determined within 1 year) was 10.1 METs (range 7.5 to 13.0) (1 MET = resting

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TABLE I Clinical Characteristics

Subject	Age (yrs)	Maximal METs Capacity	Max HR (beats/ min)	Max RPP × 10 <sup>2</sup>	Left Ventricular Impairment	CAD	MI	CABG	Medications
	54	9	141	231	Normal	1	0	0	BB, CB
1	AND ADDRESS OF THE PARTY OF THE	ALE THE STATE OF T	157	314		2	1	0	D
2	57	13		211	0	?	SE	0	0
3	77	8	109	200	0	7	1 1 1 1 1 1 1	0	D
4	70	8	127			2	0	0	BB, N
5	56	10.5	135	164	A TOTAL SE	2	0	0	BB, N
6	62	10	130	210	0	2	0	0	CB, N
7	58	11.5	152	358		1	U	THE RESERVE OF THE PARTY OF THE PARTY.	0
8	61	12	175	280	14 th 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	3		0	BB, D
9	65	10	157	317	0	2	0	+	
A STATE OF THE STA	67	12	159	259	1 1 1 1 1 1 1 1	3		0	0
10	65	7.5	160	336		3	0	+	0
11			146	262	to the second				
Mean	62.9	10.1		± 63.6					
SD	± 6.8	± 1.8	± 19.0	± 03.0					:tempolist: D =

BB =  $\beta$ -adrenergic blocker; CABG = coronary artery bypass grafting; CAD = coronary artery disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >50% obstructed); CB = calcium antagonist; D = disease (no. of coronary vessels >

metabolic rate; 3.5 ml O<sub>2</sub>/kg/min). Each subject consistently demonstrated a minimum of 1.0 mm of ST-segment depression at submaximal exercise intensities within a range of ±1 MET of their prescribed training level. None of the subjects showed ECG changes of left ventricular hypertrophy or ST-segment depression at rest, and none was taking digoxin. All subjects remained on prescribed medications during the study.

Protocol and measurements: Each subject was evaluated during 3 separate trials with at least 1 day of rest between each trial. During each session, heart rate and ECG changes were monitored using a Burdick 3-channel, 12-lead ECG recorder system. Blood pressure was determined at rest and during exercise by auscultation using a mercury manometer and modified stethoscope with a standard anesthesia diaphragm held firmly over the brachial artery by Velcro strap. Previous studies using this method have shown an excellent correlation of systolic pressure (r = 0.95) compared to simultaneous brachial intraarterial pressure recordings.<sup>12</sup>

During trial 1 (baseline), each subject performed a submaximal treadmill exercise test to determine the rate-pressure product threshold for ischemic ST-seg-

ment changes ≥1.0 mm. The speed of the treadmill was set at a brisk walking pace (3.0 to 3.5 mph) and the grade increased every 2 minutes producing +1 MET increases in exercise intensity. Blood pressure was measured at each minute and a 12-lead electrocardiogram was taken during the second minute of each stage and at the test endpoint. The baseline treadmill test was terminated when 1.0 mm of ST depression was observed. The rate-pressure product was then calculated from heart rate and systolic blood pressure measured during the last minute of the test. This value was used as a target rate-pressure product for comparison of dynamic and isodynamic exercise.

Dynamic and isodynamic exercise tests were performed in each of 2 subsequent trials (2 and 3). The sequence of the dynamic and isodynamic exercise sessions was randomly selected by each subject to avoid order of performance bias.

Dynamic exercise began with a 2-minute warmup stage at 0% followed by 3-minute stages at the same treadmill speed and grade attained during the trial 1 exercise test. Isodynamic exercise was performed by walking on the treadmill at 1.5 to 2.0 mph (mean speed

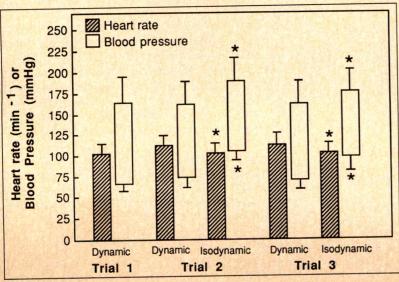


FIGURE 1. Heart rate and blood pressure responses to dynamic and isodynamic exercise. Trial 1 is baseline dynamic exercise. Trials 2 and 3 are dynamic and isodynamic exercise at equivalent rate-pressure product. Values are mean  $\pm$  1 standard deviation. \*p <0.001 for differences between dynamic and isodynamic trials.

1.6 mph) at 0% grade while carrying 15.0 to 25.0 kg (mean weight 18.8 kg) of bagged sand placed in a milk crate. The crate was held with both hands, arms slightly flexed with the crate surface against the lower abdomen and hips to maintain stability while walking. The treadmill speed, grade and amount of weight carried were adjusted for each subject to achieve the target rate-pressure product value determined during trial 1.

Blood pressure, heart rate and a 12-lead electrocardiogram were obtained during each minute of exercise. The total test duration for dynamic and isodynamic exercise was 6 minutes. Subjects rested between each mode of exercise until heart rate, blood pressure values and ECG changes returned to resting levels.

Electrocardiograms recorded during dynamic and isodynamic modes of exercise were compared at approximately equal rate-pressure product values during trials 2 and 3. One 12-lead ECG tracing was selected for each exercise mode in which the corresponding rate-pressure product was equal to or greater than the threshold seen during the trial 1 baseline treadmill exercise test. ECG tracings were coded and interpreted in random order by an investigator not involved with day-to-day data collection. ST-segment depression was expressed (in mm) according to accepted criteria of horizontal, downsloping

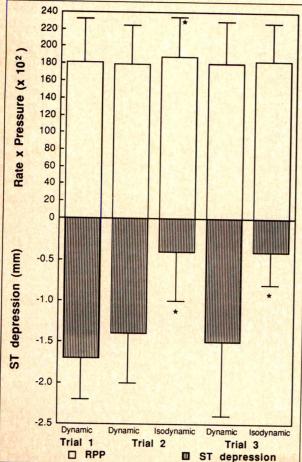


FIGURE 2. Top, rate-pressure product  $(10^2)$  and bottom, corresponding ST depression (mm). Trial 1 is baseline dynamic exercise. Trials 2 and 3 are dynamic and isodynamic exercise. Values are mean  $\pm$  1 standard deviation. \*p <0.001 for differences between dynamic and isodynamic exercise trials.

or slowly upsloping displacement from isoelectric baseline measured at 80 ms from the onset of the J point. 14

Data analysis: Interclass correlations were calculated for each minute and each mode of exercise for heart rate, systolic pressure, diastolic pressure and rate-pressure product from trials 2 and 3. One-way analysis of variance with repeated measures was used to compare heart rate, systolic blood pressure, diastolic blood pressure, rate-pressure product and ST-segment depression during dynamic and isodynamic exercise. An alpha value of ≤0.05 was accepted as significant. In the case of significant F values, post hoc testing was conducted using the Newman-Kuels test.

#### RESULTS

All subjects completed all exercise tests without difficulty or complications with the exception of subject 5 who reported angina during trials 2 and 3 of dynamic exercise.

The mean values and standard deviations for heart rate, systolic pressure, diastolic pressure, rate-pressure product and ST-segment depression for each trial are shown in Figures 1 and 2.

Heart rate and blood pressure: Systolic pressures were significantly higher (p <0.001) during isodynamic exercise compared with dynamic exercise in both trials 2 and 3 (182  $\pm$  27 and 176  $\pm$  26 vs 160  $\pm$  28 and 160  $\pm$  27 mm Hg, respectively) (Figure 1). Diastolic pressures were also significantly higher (p <0.001) during isodynamic exercise during both trials 2 and 3 (105  $\pm$  11 and 97  $\pm$  17 vs 73  $\pm$  11 and 70  $\pm$  11 mm Hg, respectively). Heart rates were significantly lower (p <0.001) during isodynamic exercise compared to dynamic exercise for both trials 2 and 3 (103  $\pm$  11 and 102  $\pm$  13 vs 112  $\pm$  12 and 112  $\pm$  14 beats/min, respectively).

Rate-pressure product and ST-segment depression: During trial 1 dynamic exercise, subjects attained a mean ST depression of 1.7 mm and a mean rate-pressure product of 18,200 (Figure 2). Dynamic exercise performed during trials 2 and 3 produced nearly identical ST depression  $(1.4 \pm 0.6 \text{ and } 1.5 \pm 0.9 \text{ mm})$  and similar rate-pressure products  $(18,000 \pm 4,500 \text{ and } 18,000 \pm 4,900)$ .

ST depression during isodynamic exercise was significantly less in trial 2 (0.4  $\pm$  0.6 mm) and trial 3 (0.4  $\pm$  0.4 mm) compared to dynamic exercise (p <0.001). The corresponding rate-pressure products in trial 2 and 3 isodynamic exercise (18,850  $\pm$  4,600 and 18,350  $\pm$  4,450) were slightly higher than the values attained in trial 2 and 3 dynamic exercise. This difference in rate-pressure product was significant during trial 2 (p <0.05).

Reliability of measurements between trials 2 and 3 was consistently high. Correlation coefficients for peak systolic blood pressure, heart rate and rate-pressure product during dynamic exercise and isodynamic exercise ranged from 0.93 to 0.99.

#### DISCUSSION

This study demonstrates that ST depression is significantly reduced during isodynamic exercise performed

at rate-pressure product values that consistently produce >1.0 mm of ST displacement during dynamic exercise. These findings indicate that the product of heart rate and systolic blood pressure may not provide an equivalent index of ischemic ST displacement during isodynamic exercise and further suggests that other hemodynamic factors may modify myocardial oxygen supply or demand during upright combined dynamic and isometric exercise.

Our study protocol produced nearly equal rate-pressure product values during dynamic and isodynamic exercise. These responses were reproducible across trials and were not altered by possible warm-up phenomenon due to order of exercise performance.15 However, the blood pressure and heart rate responses contributing to the rate-pressure product were substantially different under each exercise condition. During isodynamic exercise both systolic pressure and diastolic pressure were significantly higher and heart rate was lower compared to treadmill exercise.

The increase in diastolic pressure responses during isodynamic exercise may explain the attenuation in ST depression. Previous investigators have suggested that the higher diastolic coronary perfusion pressure produced during isometric or isodynamic exercise may augment myocardial subendocardial blood flow and thus limit ischemic changes. 7,9,16 Our data support this proposed mechanism as the most probable explanation of the attenuation of ischemic ST depression during isodynamic exercise.

Barnard et al<sup>17</sup> have also emphasized the importance of heart rate and diastolic pressure duration (diastolic pressure-time index) as a major determinant of myocardial blood flow and ischemia during sudden strenuous exercise. Our subjects attained a lower peak heart rate during isodynamic exercise, which could have permitted some additional diastolic perfusion time compared to the dynamic exercise. Since the reduction in heart rate was only 10 beats/min, it is unlikely that this was an important mechanism in reducing ST depression in this

Other hemodynamic factors may have contributed to the reduction in ST depression during isodynamic exercise. Increased intrathoracic pressure caused by alterations in breathing pattern or breath holding during upright weight carrying could have reduced central venous return and decreased left ventricular diastolic volume and wall tension, which would also minimize subendocardial ischemia. 18,19 Pepine and Nichols 19 recently showed that voluntary Valsalva maneuvers frequently produced a prompt relief of spontaneous or exercise-induced anginal symptoms. They attributed this response to reductions in left ventricular size and filling pressure, which were measured during Valsalva maneuver. We attempted to control the potential effects of breath holding on intrathoracic pressure and venous return by instructing subjects to maintain regular breathing patterns during isodynamic exercise. However, some degree of increased intrathoracic or abdominal pressure

probably occurred in most subjects due to additional recruitment of intercostal and diaphragmatic muscle tension during weight carrying.

Isometric exercise is usually discouraged in patients with coronary artery disease because of the assumed increase in myocardial oxygen demand created by elevated systolic blood pressure. Our study shows that shortterm combined isometric and dynamic exercise performed at submaximum rate-pressure product levels is well tolerated and produces minimal evidence of ST depression in patients with stable coronary artery disease. We emphasize that our patient population had a high exercise capacity and a low incidence of anginal symptoms. Accordingly, our findings may not extend to patients with more severe coronary disease or low exercise capacity.

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#### Relation of Syncope in Young Patients with **Wolff-Parkinson-White Syndrome to Rapid Ventricular Response During Atrial Fibrillation**

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Syncope in patients due to Wolff-Parkinson-White (WPW) syndrome may be related either to a rapid rate of supraventricular tachycardia or to rapid ventricular response over the accessory pathway during atrial fibrillation (AF). From 1982 to 1987, 74 patients ≤25 years old (mean age 12.6 years) with WPW syndrome on electrocardiogram underwent electrophysiologic study. Of the 74 patients, 14 (19%) had a history of syncope. During electrophysiologic study 9 of 14 patients with syncope had sustained (>5 minutes or requiring termination due to hypotension) AF. Of the remaining 5 patients, 3 had inducible nonsustained AF and 2 had no AF. None of the 60 patients without syncope developed sustained AF; 34 had nonsustained and 26 had no AF. Occurrence of sustained AF had a sensitivity of 64% and specificity of 100% for history of syncope. All patients with syncope and AF (12) had a short RR interval between 2 consecutive preexcited QRS complexes during AF at ≤220 ms, in contrast to 9 of 34 patients without syncope (p <0.001, sensitivity 100%, specificity 74%). No patient with a short RR interval between 2 consecutive preexcited QRS complexes during AF of >220 ms had a history of syncope. Thus, in these young patients with WPW syndrome, occurrence of AF with a rapid ventricular response during electrophysiologic study correlated well with a history of syncope and may be the cause of syncope in most patients. Electrophysiologic study may be helpful in identification of young patients with WPW at risk for syncope.

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yncope in young patients due to the Wolff-Parkinson-White (WPW) syndrome may be related either to a rapid rate of reciprocating supraventricular tachycardia or to a rapid ventricular response over the accessory pathway during atrial fibrillation (AF). Pediatric patients with WPW syndrome may develop atrial flutter or AF with the onset of adolescence or young adulthood, but the age at which AF becomes a clinical problem is undefined. AF has been reported to occur spontaneously in 11 to 39% of adult WPW patients.2-5 The occurrence of AF in patients with WPW syndrome >12 years old has only been reported rarely.6 However, severe symptoms due to AF, such as syncope, ventricular fibrillation and sudden death, 7,8 may occur in young patients. Therefore, it would be helpful if prediction of these events was possible. The present study characterizes the sensitivity and specificity of electrophysiologic findings to identify young patients with WPW syndrome and syncope (specifically to assess the number of patients with syncope who had either spontaneous or inducible AF during electrophysiologic study).

#### **METHODS**

Patient population: At Texas Children's Hospital from 1982 to 1987, 74 patients ≤25 years old with WPW syndrome on routine electrocardiogram underwent electrophysiologic study after informed consent was obtained from each patient, or the patient's parents if the patient was under 18 years old.

Electrophysiologic study: All patients underwent electrophysiologic study in the postabsorptive state after premedication with meperidine (2 mg/kg) and promethazine (1 mg/kg). All antiarrhythmic drugs were discontinued at least 5 half-lives before the study.

After electrode catheters had been placed in the coronary sinus, high right atrium, right ventricular apex and His bundle area, programmed atrial and ventricular stimulation were performed as previously described.9 The location of the accessory pathway was determined by endocardial mapping.9,10 In 7 patients AF occurred spontaneously after supraventricular tachycardia. In the remaining 67 patients, induction of AF was attempted by atrial stimulation. Single and double atrial extrastimuli were introduced into paced atrial rhythm. If the atrial extrastimuli were unsuccessful, rapid atrial pacing was performed beginning at a cycle length of 300 ms with successive shortening of the cycle length in 20-ms

steps until sustained AF was induced or a cycle length of 200 ms was reached. Rapid atrial pacing was performed once at each cycle length. Pulse duration and amplitude remained constant. Duration of stimulation was 15 seconds for each cycle length. In 10 patients, extrastimuli were introduced without rapid atrial pacing.

AF was defined as sustained if it lasted at least 5 minutes or required termination due to hypotension.

The anterograde effective refractory period of the atrioventricular accessory pathway was defined as the longest A<sub>1</sub>-A<sub>2</sub> interval that failed to conduct with a delta wave and was determined at 2 different pacing cycle lengths (usually 500 and 400 ms). The anterograde effective refractory period of the accessory pathway value nearest the site of the accessory connection obtained at the shorter pacing cycle length was used for comparison and statistical analysis.

Statistical analysis: Contingency tables were evaluated by Fisher exact test or chi-square analysis. Numerical data were compared using the Student t test for unpaired data and analysis of variance, respectively; p <0.05 was considered to indicate a significant difference.

#### RESULTS

Patient characteristics: The study group consisted of 74 patients ranging in age from 1.5 to 25 (mean 13) years at the time of electrophysiologic study. Congenital heart disease was found in 16 of the 74 (22%) patients; the remaining 58 patients had a structurally normal heart. All patients underwent electrophysiologic study either because of syncope or recurrent episodes of symptoms and were studied either to determine optimal medical management or location of the accessory pathway for subsequent surgery. The findings do not represent an unselected sample but are appropriate for this comparison of patients with and without syncope.

**Symptoms:** Of the 74 patients, 14 (19%) presented with a history of syncope at a mean age of 14 (range 1.5 to 24) years. Syncope was the first symptom in 2 patients; the other 12 had had previous episodes of rapid palpitations. The cause of syncope was documented ventricular fibrillation in 2 patients; in the remaining 12 patients its cause was unknown, but presumed to be related to WPW syndrome. None of these 14 patients had any evidence of a cerebral or metabolic disorder. The remaining 60 patients had recurrent episodes of palpitations or dizziness. They underwent electrophysiologic study at a mean age of 12.3 (2 to 25) years.

Occurrence of syncope was not related to the age at electrophysiologic study, incidence of congenital heart disease, frequency of supraventricular tachycardia, incidence of multiple accessory pathways, pathway location or cycle length of supraventricular tachycardia during electrophysiologic study.

Electrophysiologic findings: ANTEROGRADE EFFECTIVE REFRACTORY PERIOD OF THE ACCESSORY PATHWAY: In patients with a history of syncope, the anterograde effective refractory period of the accessory pathway was sig-

nificantly (p <0.01) shorter (230  $\pm$  39 ms, mean  $\pm$  standard deviation) than in those without syncope (284  $\pm$  69 ms). The anterograde effective refractory period of the accessory pathway was <250 ms in 10 of the 14 patients with syncope but also in 20 of the 60 patients without syncope (p <0.01, sensitivity 71%, specificity 67%).

ATRIAL FIBRILLATION: During electrophysiologic study, 9 of the 14 patients with a history of syncope developed sustained AF. In 7 of these 9 patients, supraventricular tachycardia degenerated spontaneously into AF, and in 2 patients, AF was induced by atrial stimulation. In all of these 9 patients, AF had to be terminated. Of the remaining 5 patients with syncope, 3 had inducible nonsustained AF and 2 had no AF. No patient without syncope developed sustained AF: 34 of the 60 patients had inducible nonsustained AF and 26 patients had no AF. Occurrence of sustained AF had a sensitivity of 64% and a specificity of 100% to identify patients with a history of syncope. In the 2 patients with syncope in whom AF did not occur spontaneously but had to be induced, double atrial extrastimuli and rapid atrial pacing were required in 1 patient each. In the remaining 5 patients with syncope even rapid atrial pacing failed to induce sustained AF. In the 34 patients without syncope who had nonsustained AF, only single and double atrial extrastimuli were delivered in 7 patients. Additional rapid atrial pacing was performed in the remaining 27 patients and failed to induce sustained AF. In the 26 patients without syncope and without any AF, maximal atrial stimulation protocol consisted of double extrastimuli in 2 and rapid atrial pacing in the remaining 24 patients.

Among the groups of patients who had sustained, nonsustained or no AF, no significant differences were found in cycle length or frequency of supraventricular tachycardia, and age at electrophysiologic study.

Patients with both syncope and either sustained or nonsustained AF had a significantly (p <0.01) shorter (198  $\pm$  16 ms) RR interval between 2 consecutive preexcited QRS complexes during AF than patients without syncope (279  $\pm$  71 ms). All patients with syncope exhibited the shortest RR interval between 2 consecutive preexcited QRS complexes during AF of  $\leq$ 220 ms in contrast to 9 of 34 patients without syncope (p <0.001, sensitivity 100%, specificity 74%).

In the 46 patients who developed sustained or nonsustained AF, a significant (p <0.001) correlation (r = 0.96) was found between the anterograde effective refractory period of the accessory pathway and a short RR interval between 2 consecutive preexcited QRS complexes during AF. However, there was considerable variability in some patients. Of the 21 patients with a short RR interval between 2 consecutive preexcited QRS complexes during AF of ≤220 ms, the anterograde effective refractory period of the accessory pathway was found to be >250 ms in 3 patients (14%). Conversely, of the 26 patients with a relatively long anterograde effective refractory period of the accessory pathway (>250 ms), 3 (12%) had a very short RR in-

terval between 2 consecutive preexcited QRS complexes during AF ( $\leq 220 \text{ ms}$ ).

#### DISCUSSION

Syncope and ventricular fibrillation are the most dramatic events in patients with the WPW syndrome. 4,11 The relation of syncope and ventricular fibrillation to the anterograde conduction properties of the accessory pathway in terms of a rapid ventricular response during AF has been demonstrated in several previous studies, 2,3,12-14 but data have mainly been obtained from adult patients. The occurrence of ventricular fibrillation and sudden death in adults with WPW syndrome is a rare event, 13 and its likelihood in children is even rarer. A history of syncope itself has been demonstrated to be a risk factor for developing ventricular fibrillation.<sup>15</sup> In our study group, 14 of the 74 young patients had a history of syncope; 2 patients had no inducible AF even after performing rapid atrial pacing, and therefore, syncope was possibly not related to AF. Syncope could be explained in 1 of these 2 patients by a very short cycle length of supraventricular tachycardia of 240 ms; syncope remained unexplained in the second patient, who had a normal heart and a cycle length of supraventricular tachycardia of 205 ms.

AF occurred in 12 of the 14 patients with syncope. All of these 12 patients had a very short RR interval between 2 consecutive preexcited QRS complexes during AF (≤220 ms). In light of the demonstrated correlation between clinical arrhythmias and electrophysiologic findings in patients with WPW, 1,16 syncope may be explained by a rapid ventricular response during AF in the majority of our patients.

In our study group of young patients with WPW syndrome and a mean age of 12.6 years, the anterograde effective refractory period of the accessory pathway correlated well with a short RR interval between 2 consecutive preexcited QRS complexes during AF, as has been demonstrated by Wellens and Durrer.<sup>2</sup> As previously reported in adult patients, however, the anterograde effective refractory period of the accessory connection was of little value in identifying patients with severe symptoms such as a history of syncope or ventricular fibrillation. 12,13 Even separation of patients according to an anterograde effective refractory period of the accessory connection of ≤250 ms was of low sensitivity and specificity.

In accordance with the report of Klein et al<sup>12</sup> on mostly adult patients with WPW syndrome and ventricular fibrillation, a short RR interval between 2 consecutive preexcited QRS complexes during AF was a useful variable in distinguishing our patients with syncope from those without syncope. In all our young patients with syncope and AF, the shortest RR interval between 2 consecutive preexcited QRS complexes during AF was ≤220 ms, providing a sensitivity of 100%. Specificity was 74%, and 9 of 34 patients without syncope had a very short RR interval between 2 consecutive preexcited QRS complexes during AF of ≤220 ms. Using this measure of a short RR interval between 2 consecutive preexcited QRS complexes during AF of 220 ms, elec-

trophysiologic testing in our young patients provided higher sensitivity and specificity to identify patients with severe symptoms than in adults.13

AF has been shown to be inducible in almost all asymptomatic adult patients with WPW syndrome. 17 In pediatric patients without WPW syndrome and a structurally normal heart, the ability to induce AF during electrophysiologic study has been reported to increase with advancing age. 18 In a group of 15 adolescents (age 12 to 20 years) with WPW syndrome studied by Sterba and Maloney, all patients developed AF during electrophysiologic study. In all those patients, rapid atrial pacing had been performed, unless AF occurred spontaneously or was induced by atrial extrastimuli. The discrepancy between our results and those of Sterba and Maloney1 may be explained by the younger age of our patients (mean age 12.6 years, range 1.5 to 25 years), as AF has been shown to occur more often in older patients.19 It is unlikely that it is related to the few patients in the present study group who did not have rapid atrial pacing. Our results are in accordance with the findings of Milstein et al,17 who found that AF was difficult to induce and always self-terminating in their group of asymptomatic patients. Inability to induce AF in many of our young patients without syncope may be related to the absence of atrial electrical instability due to young age or the small size of the child's atrium.

Only patients with a history of syncope developed sustained AF. All of them, however, had a very rapid ventricular response (short RR interval between 2 consecutive preexcited QRS complexes during AF of ≤220 ms). Therefore, it is not possible on the basis of this study to determine if the occurrence of sustained AF during electrophysiologic study in a patient ≤25 years old is an independent variable in identifying those who are at risk of developing syncope.

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#### Value of Esophageal Pacing in Evaluation of Supraventricular Tachycardia

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Esophageal stimulation was performed in 40 patients who had spontaneous paroxysmal supraventricular tachycardias (SVTs). The purpose of this study was to look for the most sensitive stimulation protocol and criteria that would help to define the mechanism of reentry. In 20 patients (group I) atrial pacing up to second-degree atrioventricular block was performed under control conditions and isoproterenol, and SVT was induced in 14 patients (70%), 11 in the control state and 3 while receiving isoproterenol. In 20 patients (group II) atrial pacing and programmed atrial stimulation using 1 and 2 extrastimuli delivered at 2 cycle lengths (600 and 500 ms) was performed in the control state and while receiving isoproterenol. SVT was induced in all patients, in 13 patients in the control state and in 7 while receiving isoproterenol. Programmed stimulation always induced SVT and was the only method capable of tachycardia induction in 14 patients. The mechanism of SVT could be established in 91%. The measurement of the ventriculoatrial interval was the most useful sign to define the site of reentry. Occurrence of a bundle branch block helped to delineate the mechanism in 4 patients. When a positive P wave in V1 preceded the esophageal atrial electrocardiogram, it suggested that there was reentry through a leftsided accessory atrioventricular connection in 6 patients. SVT could always be induced by programmed atrial stimulation in the control state and under isoproterenol. The location of the P wave in V<sub>1</sub> compared to the ventriculogram and the esophageal electrocardiogram helped to define the mechanism of tachycardia.

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he utility of recording electrocardiograms from the esophagus had been recognized for over 50 years1 before Shafiroff and Linder2 successfully used the esophagus as an extracardiac pacing site. More recently, Gallagher et al3 recorded ventriculoatrial intervals from the esophagus during supraventricular tachycardia (SVT) to help define the mechanism of SVT. Gallagher et al4 also used the same esophageal lead to induce SVT by atrial pacing. This study evaluates the sensitivity of esophageal pacing in the induction of SVT, to assess the methods required for inducing SVT in patients with documented SVT, and to assess the utility of esophageal pacing in identifying the reentrant circuit.

#### **METHODS**

Patients: The study group consisted of 46 patients, 27 men and 19 women, mean age 45 years (range 11 to 84), who had been admitted for documented SVT. Twelve patients had the Wolff-Parkinson-White syndrome.

Transesophageal study: Antiarrhythmic therapy was discontinued for at least 5 half-lives before testing. An intravenous catheter was inserted before the procedure. The possible discomfort induced by esophageal pacing was explained to patients before the test. Patients were studied in the postabsorptive state and were not sedated for this procedure. A bipolar permanent transvenous electrode (Medtronic 6992 or Prothia 8), with electrodes spaced at 29 mm, was used. With the patient in the supine position, the bipolar electrode was passed through the mouth into the distal esophagus and its position adjusted until the proximal electrode showed the greatest amplitude.

The stimulation threshold was adjusted to be in the range of 10 to 16 ms width and 10 to 20 mA amplitude. The stimulus amplitude slightly in excess of that resulting in consistent atrial capture was selected. For the stimulation we used either a custom-made stimulator (J. Kasell, Duke University, Durham, North Carolina) or a standard electrophysiologic stimulator (Explorer 2000, Ela), connected to an Ela pulse amplifier that can deliver pulses of 20 ms width and 29 mA output. For the recording, the Siemens electrocardiographic device (Siemens Elema Mingograph) was used. The classic filtering used for intracardiac recording was used for recording of the esophageal electrocardiogram. It was not possible to perform the study in 6 patients; 3 patients refused the electrode and 3 patients did not tolerate stimulation. We point out that esophageal pacing diffi-

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Pt	Age (yrs), Sex	ECG	Basal AP	IS AP	Beg	VA (ms)	BBB	ATP	Reentry
1	57, F	N	SSVT		AV†	<70		0	AVN
2	33, M	N	SSVT			200→120	Permanent BBB	VA↓	AVN
3	23, F	WPW(A)	SSVT			100	LBBB(+)	0	AC
4	31, F	N	0	0					
5	26, M	N	0	0					
6	42, F	N			AV†	<70		0	AVN
7	57, M	N				150		0	
8	28, F	N	0	SSVT	AV†	<70 variable VCL		0	AVN
9	47, M	N			AV†	variable 150→240	LBBB(0) RBBB(0)		AVN
10	84, M	N		SSVT	AV†	AV dissociation or <70			AVN
11	22, M	WPW(C)	0	(AT)					
12	54, M	N	SSVT			<70		0	AVN
13	50, F	WPW(A)	0	0	AV†				
14	74, M	N	SSVT			<70			AVN
15	23, M	RBBB	SSVT		AV <sup>†</sup>	170			
16	16, F	N	0	0					
17	37, M	WPW (A)	0	NSSVT		120 alternans			AC
18	58, M	N	SSVT		AV†	<70		0	AVN
19	76, M	N	SSVT			110	LBBB(+)		AC
20	58 M	N	0	0					

AC = accessory AV connection using retrograde conduction; AT = atrial tachycardia; ATP = adenosine triphosphate; AVN = AV node; AV† = abrupt increase in AV interval; Basal AP = basal atrial pacing; BBB = bundle branch block; Beg = beginning of tachycardia; ECG = electrocardiogram; IS AP = atrial pacing under isoproterenol; LBBB = left BBB; N = normal; RBBB = right BBB; Reentry = site of reentry; SSVT = sustained paroxysmal supraventricular tachycardia; VA = measurement of ventricularial interval; VA↓ = decrease in VA interval; VCL = ventricular cycle length; WPW = Wolff-Parkinson-White syndrome; + = increase in cycle length induced by BBB; 0 = absence of CL modification; 0 = absence of sign permitting mechanism of reentry to be defined.

culties have principally been noted in the patients studied first. There were 5 stimulation failures among the first 10 patients studied. In the remaining 40 patients esophageal pacing was done according to 2 stimulation protocols that were consecutively executed; in the first 20 patients only the custom-made stimulator was available and they were studied by protocol I. In the next 20 consecutive patients the programmable stimulator was available and they were studied by protocol II.

**Protocol I:** In 20 patients we tried to induce SVT by incremental atrial pacing at progressively higher rates up to the cycle length at which second-degree atrioventricular block occurred, and by short bursts of atrial pacing at 200 ms. In 8 patients who had inducible sustained tachycardia in the basal state and in whom carotid massage was inefficacious, we attempted to stop the tachycardia by injection of 10 mg of adenosine triphosphate to study the way in which SVT terminated. If SVT could not be induced as described, isoproterenol  $(0.02 \text{ to } 1 \mu \text{g/min})$  was infused to increase the sinus rate to at least 130 beats/min and the pacing protocol was repeated.

**Protocol II:** In 20 patients, incremental atrial pacing to second-degree atrioventricular block, and programmed atrial stimulation at a basic cycle length of 600 and 400 ms with the introduction of 1 and 2 extrastimuli, were performed (protocol II). Premature stimuli (S<sub>2</sub>) were initiated after every 8 paced complexes beginning in late diastole, and at progressively closer coupling intervals until atrial refractoriness occurred. When the P wave was not clearly visible, we used an S<sub>2</sub> to the point of atrioventricular block. Then the shortest cou-

pling interval  $(S_1-S_2)$  resulting in consistent atrial capture was chosen, and a second premature stimulus  $(S_3)$  was introduced, beginning with an  $S_2-S_3$  interval 100 ms longer than the  $S_1-S_2$  interval. The  $S_2-S_3$  interval was shortened by 10-ms decrements until  $S_3$  no longer resulted in atrial depolarization.

Ten mg of adenosine triphosphate was injected during tachycardia in 5 patients who had inducible sustained tachycardia in the basal state and in whom carotid massage did not stop tachycardia. If tachycardia was not initiated under basal conditions, isoproterenol (0.02 to  $1 \mu g/min$ ) was infused to increase the sinus rate to at least 130 beats/min, and the pacing protocol was repeated. In 7 patients who had inducible sustained tachycardia in the basal state, isoproterenol was infused to study its effect on the properties of a patent or suspected accessory atrioventricular connection.

Identification of the reentrant circuit: When the tachycardia SVT had been induced, the esophageal electrocardiogram was recorded. Tachycardia was terminated either by carotid massage or esophageal pacing or adenosine triphosphate in 13 patients; we tried to reinduce tachycardia 1 to 3 times to obtain transitory functional bundle branch block.

The following variables were observed<sup>5</sup>: behavior of anterograde conduction at the onset of tachycardia; relation of atrial and ventricular activation at the onset of tachycardia, and during tachycardia; influence of functional bundle branch block on the rate of tachycardia; morphology and place of P wave in lead V<sub>1</sub> compared to that of esophageal recording; and influence of adenosine triphosphate on the ventriculoatrial interval.

TABLE II Results of Esophageal Stimulation in Group II Age (yrs) IS VA Pt Sex ECG AP S1S2 S1S2S3 AP S1S2 S1S2S3 Beg (ms) ATP Reentry 80. M SSVT SSVT SSVT <70 AVN 2 74, F 0 SVT SVT 3 69, M SSVT SSVT SSVT AVT <70 AVN >70 variable WPW(A) 40. F 0 0 SSVT 0 SSVT SSVI 5 48. F 0 0 SSVI 0 0 AV1 <70 AVN 6 18. F N 0 0 0 0 SSVT SSVT AVT <70 AVN 7 76, F WPW(A) 0 SSVT SSVT 0 SSVT SSVT 100 RBBB(0) 0 AC 8 40, F N 0 0 0 0 0 SPT 200 SN 31, M WPW(A) 0 0 0 0 0 SSVT 120 RBBB(0) AC 10 58. M N AT SSVT SSVT AVT <70 0 AVN 11 53. M 0 0 0 0 SSVT SSVT 110 RBBB(0) 12 11, M WPW(A) 0 NSSVI 0 0 SSVT SSVT 100 LBBB(+) AC Alternans 13 22, M WPW(C) **NSSVT** SSVT AT SSVT 0 SSVT 140 RBBB(+) AC 14 66, M 0 SSVT SSVT 150 15 46, F N 0 SSVT SSVT SSVT 0 SSVT AVT <70 RBBB(0) AVN Alternans 16 40. F WPW(+) SSVT SSVT SSVT 0 SSVT SSVT 125 RBBB(0) AC Alternans 17 56. M WPW(A) NSAT SSVT SSVT NSAT 0 SSVT 150 Permanent AC RBBB 18 83. M 0 SSVT SSVT <70 0 AVN irregular 19 15. M 0 0 SSVT SAT 170 0 Alternans 20 17. F WPW(A) SAT SSVT 140 RBBB(0) AC LBBB(+)

Pagntry SN = regetty in circus node: C1C2 = regetty and a bid of the circus an	the same of the sa
definity of a feeting in sinus flode, 5152 = programmed atrial stimulation using one extrastimuli delivored at 2 gyala langtha, 616063	
Réentry SN = reentry in sinus node; S1S2 = programmed atrial stimulation using one extrastimuli delivered at 2 cycle lengths; S1S2S3 = programmed atrial stimulation usistimuli delivered at 2 cycle lengths; S1S2S3 = programmed atrial stimulation usistimuli delivered at 2 cycle lengths; S1S2S3 = programmed atrial stimulation usis	ng 2 ev-
stimuli delivered at 2 cycle lengths. Other abbreviations as in Table I.	IIB L CA
and a control of the	

	Contro	ol State				Isoproterenol					
	No.	AP	S <sub>1</sub> S <sub>2</sub>	S <sub>1</sub> S <sub>2</sub> S <sub>3</sub>	Total	No.	AP	S <sub>1</sub> S <sub>2</sub>	S <sub>1</sub> S <sub>2</sub> S <sub>3</sub>	Total	Total
Group I	20	11			11 (55%)	9	3			3	14
Group II	20	3	10	12	13 (65%)	14	3	7	12	13 (93%)	20 (100%

Tachycardia due to reentry within the atrioventricular node was presumed to be present if tachycardia was induced after an abrupt increase in atrioventricular interval, and the ventriculoatrial interval (onset of ventricular depolarization to rapid deflection on the esophagoatrial waveform) was ≤70 ms.<sup>3,6</sup>

Tachycardia due to reentry within an accessory atrioventricular connection was presumed to be present if the tachycardia rate was regular, there was no evidence of atrioventricular dissociation, the ventriculoatrial interval was >70 ms<sup>3</sup> and the left or right bundle branch block increased the cycle length of tachycardia.

#### RESULTS

Current threshold: The minimal pulse duration at which successful capture occurred ranged from 10 to 18 ms; to avoid delivery of an excessively high current the duration of 16 ms was chosen for most of the patients. The current threshold at this pulse duration ranged

from 10 to 25 mA (mean  $18 \pm 3$ ). Successful capture was obtained in all patients; however, discomfort accompanied delivery of currents in excess of 20 to 25 mA, and the stimulation protocol could not be repeated in 5 patients.

Induction of tachycardia: Using incremental pacing (protocol I) in the control state and under isoproterenol, paroxysmal tachycardia was induced in 14 of 20 patients (Tables I and II, Figure 1). In 1 of them tachycardia was transient (<30 seconds); in other patients tachycardia was sustained and required stimulation to stop it. Induction was transient in the control state in 11 patients, and after isoproterenol in 3 patients (Table III).

Using incremental pacing and programmed stimulation in the control state and while the patient received isoproterenol (protocol II), paroxysmal tachycardia was induced in all patients (Tables II and III, Figures 2 and 3). Induction of SVT was obtained in 13 patients in the

control state and 7 patients while receiving isoproterenol. In 7 patients who had inducible tachycardia in the control state and who received isoproterenol, the tachycardia was also reproduced while receiving isoproterenol except in 1 patient in whom a sustained atrial tachycardia was induced. SVT induction required programmed stimulation in 13 patients. The mode of initiation is listed in Table III.

was induced in 34 patients; the type of reentry was proven in 31 and only presumed in 3 patients (Tables I and II).

The patterns of retrograde atrial activation during tachycardia were the clearest signs of the type of reentry. The occurrence of atrial deflection during ventricular activation excludes the participation of an atrioventricular accessory connection to the reentry, and was noted in 14 of our patients (Figures 1 and 3). All these patients showed a sudden increase in atrioventricular time at the initiation of tachycardia.

In 20 patients, atrial activation followed the ventriculogram. Some findings disproved the participation of an accessory AV connection during SVT in 5 patients and suggested specific diagnoses that could be discussed. In 2 patients the ventriculoatrial interval was long (>200 ms) and fixed, but the morphology of the P wave was similar to that of the sinus P wave. Reentry was presumed to be present in sinus node. In 2 patients the ventriculoatrial interval was variable and this fact excluded the participation of an accessory atrioventricu-

lar connection in the reentry (Figure 4). One of these patients had 2 forms of tachycardia and in 1 of them the ventriculoatrial interval was <70 ms, excluding an accessory atrioventricular connection with decremental properties. In 1 patient the ventriculoatrial interval did not change during tachycardia; there was retrograde activation of atria. The injection of 10 mg of adenosine triphosphate was responsible for an abrupt decrease in ventriculoatrial interval, without any change in ventricular cycle length (Figure 5).

In the 15 remaining patients the participation of an accessory atrioventricular connection was suggested. However, this participation could be proved by a patent Wolff-Parkinson-White syndrome, by influences of a functional bundle branch block in only 11 patients or by both. In 5 patients a ventriculoatrial interval of >70 ms was the only sign of a reentry through an accessory pathway. In 1 of these patients an intracardiac recording excluded the presence of a Kent bundle and thus proved the existence of a reentry in atrioventricular node. In the other 4 the presence of an accessory atrioventricular connection was demonstrated by intracardi-

ac recording.

The influences of functional bundle branch block on the rate of tachycardia were noted; the occurrence of bundle branch block was less frequent than in the study of Goldstein et al<sup>7</sup>; only 12 patients showed transient bundle branch block at the onset of tachycardia and in only 2 was reentry presumed to be located in the atrioventricular node. In 10 patients the ventriculoatrial in-

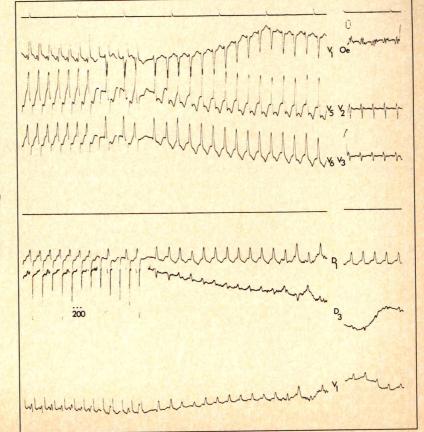


FIGURE 1. Patient 5 of group II. Induction of supraventricular tachycardias by atrial pacing under isoproterenol. Esophageal electrocardiogram occurs in ventriculogram. Lead D1 corresponds to lead limb I.

terval was >70 ms. In 4 of these patients the increase in cycle length, associated with the bundle branch block, suggested the localization of an atrioventricular accessory connection site, which was right in 1 (Figure 6) and left in 3 (Figure 7) patients. Changes in ventriculoatrial interval during bundle branch block were not visible.

Therefore, the information provided by transient bundle branch block changes was valuable in only 4 of the 34 patients with tachycardia.

QRS alternans was observed in 5 patients, 1 with reentry in the atrioventricular node, 2 with reentry through an accessory atrioventricular connection and 2 with indeterminate reentry.

The injection of adenosine triphosphate during tachycardia did not help to determine the type of reentry except in 1 patient who presented an abrupt decrease in the ventriculoatrial interval without any change in the ventricular cycle length (Figure 5).

The morphology of the P wave in lead  $V_1$  and its position compared to that of the esophageal atrial electrocardiogram was useful in determining the site of reentry (Figure 8). The P wave in  $V_1$  slightly preceded the

esophageal electrocardiogram in 2 patients having reentry in the atrioventricular node and a ventriculoatrial interval >70 ms, in 1 patient having a reentry through a right-sided accessory atrioventricular connection and in 2 patients having a reentry through a septal accessory atrioventricular connection. In 7 patients, the esophageal electrocardiogram preceded the P wave, which was clearly positive. In 5 of these patients, the presence of a left lateral accessory atrioventricular connection could be established by intracardiac recording suggesting that the preceding esophageal electrocardiogram on the positive wave in lead V1 could be a sign of reentry through a left-sided accessory atrioventricular connection. Of the 4 patients who had a ventriculoatrial interval of >70 ms and no other sign of reentry through an accessory atrioventricular connection, the precession of esophageal electrocardiogram on P wave in V1 was found in 2.

#### DISCUSSION

The major finding of this study is that transesophageal atrial pacing always induces tachycardia in patients with SVT if programmed atrial stimulation and

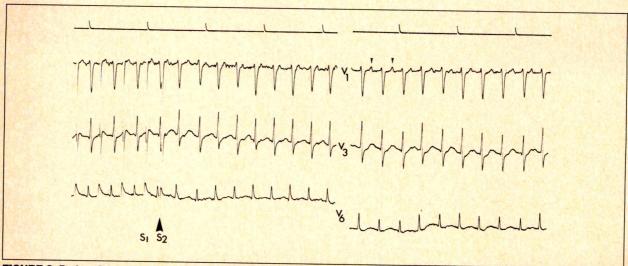


FIGURE 2. Patient 3 of group II. Induction of SVT by 1 extrastimulus delivered on driven rhythm. P wave in  $V_1$  is noted after QRS complex but ventriculoatrial interval is variable. Esophageal electrocardiogram could not be correctly registered at this time and did not permit confirmation of the variations of the ventriculoatrial interval.

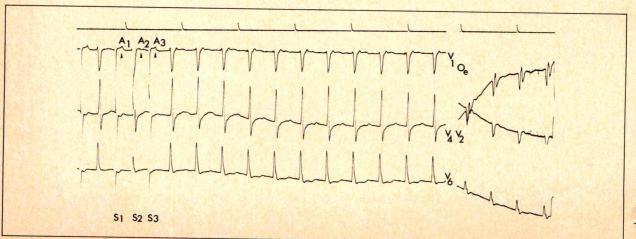


FIGURE 3. Patient 1 of group II. Induction of supraventricular tachycardias by extrastimuli after abrupt increase in AV interval. Atrial electrocardiogram occurs in QRS complex.

isoproterenol infusion are used. The mechanism of reentry was demonstrated in 91% of our patients; tachycardia due to reentry within the atrioventricular node was presumed to be present in 16 of 34 patients (47%). Reentry within the sinus node was presumed to be present in 2 of 34 patients (6%); tachycardia due to reentry within an accessory atrioventricular connection was presumed to be present in 13 of 34 patients (35%).

The utility of transesophageal pacing to initiate tachycardia has been demonstrated in patients with previous electrocardiographic documentation of tachycardia.3,7-9 Different studies use different stimulation protocols: Gallagher et al<sup>3,4</sup> induced tachycardia by rapid pacing in 35 of 38 patients (90%). Pongiglione et al9 used incremental pacing, burst pacing and single extrastimulus introduced into normal sinus rhythm and at 3 cycle lengths in the control state; tachycardia was induced in 16 of 28 patients who had palpitations (57%). A similar protocol was used in the study of Benson et al.10 The protocol used by Goldstein et al7 consisted of programmed atrial stimulation and atrial pacing. Tachycardia was initiated in all of the 58 infants studied (100%). All these infants, however, had an accessory atrioventricular connection.

In our study in the control state, incremental pacing initiated tachycardia in 14 of 40 patients (35%). A single extrastimulus delivered at 2 cycle lengths initiated tachycardia in 10 of 20 patients (50%). Two extrastimuli were required in 3 of 20 patients. Tachycardia

induced by incremental pacing was always induced by programmed stimulation. Isoproterenol infusion was necessary in other patients to reproduce the tachycardia.

Benson et al<sup>10</sup> and Pongiglione et al<sup>9</sup> used the technique of infusing small doses of isoproterenol, but tachycardia was initiated in only 4 of 12 patients. In a previous study concerning intracardiac recording, <sup>11</sup> we demonstrated the excellent sensitivity and specificity of isoproterenol infusion in inducing adrenergic-related paroxysmal tachycardias. In the present study only isoproterenol infusion and incremental pacing or programmed stimulation permitted the initiation of a paroxysmal tachycardia in 10 of 34 patients with inducible tachycardia. The evaluation of the mechanism of reentry may be suggested by some signs that have been known for many years. <sup>5,6,12-14</sup>

The occurrence of atrial activation during the ventriculogram of tachycardia excludes the presence of an accessory pathway. When atrial activation follows the QRS complex, the participation of an accessory atrioventricular connection is suggested but other observations are required to confirm its presence by intracardiac recording. Patterns of retrograde atrial activation and effects of premature ventricular extrastimuli on the tachycardia provide valuable information to identify an accessory atrioventricular conduction.

The value of the 12-lead electrocardiogram in differentiating between atrioventricular nodal reciprocating

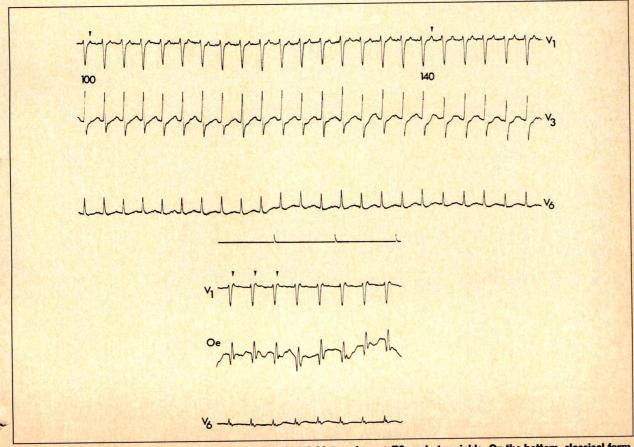


FIGURE 4. Patient 3 of group II. On the top the ventriculoatrial interval was >70 ms but variable. On the bottom, classical form of tachycardia in AV node with P wave in QRS complex.

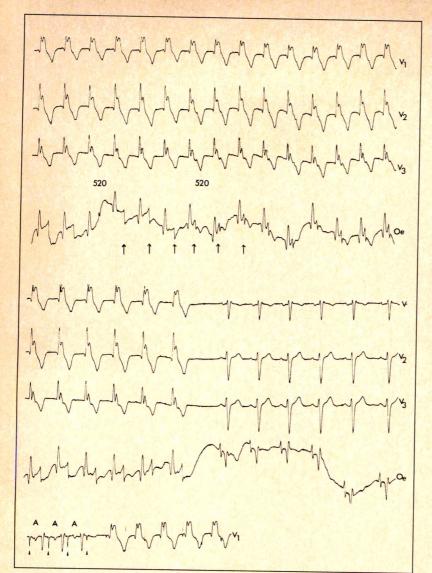


FIGURE 5. Patient 2 of group I. Abrupt decrease in ventriculoatrial interval after injection of adenosine triphosphate, without change in ventricular cycle length. The second electrocardiogram shows the abrupt termination of tachycardia after injection of 5 mg of verapamil. The third electrocardiogram (bottom) shows the induction of tachycardia by atrial pacing.

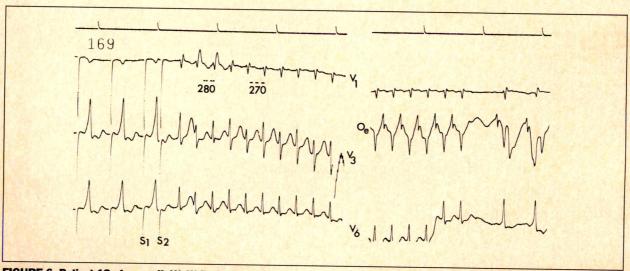


FIGURE 6. Patient 13 of group II. Wolff-Parkinson-White syndrome (type C) in sinus rhythm. Induction of reciprocating tachycardia by 1 extrastimulus. Transient right bundle branch block (RBBB) at the beginning of tachycardia; when RBBB disappears the cycle length decreases, showing that the retrograde conduction uses a right-sided accessory atrioventricular connection. However, changes in ventriculoatrial interval during bundle branch block were not obvious and the accessory atrioventricular connection was only suggested. Right, supraventricular tachycardias terminated spontaneously, and during tachycardia, ventriculoatrial interval was obvious (140 ms).

tachycardia and circus movement atrioventricular tachycardia using a retrograde accessory atrioventricular connection has recently been demonstrated. 15,16 Sometimes, however, the occurrence of a rapid tachycardia does not always permit the electrocardiogram to be analyzed correctly. The onset of tachycardia after an abrupt increase in the atrioventricular interval suggests a reentry within the atrioventricular node. 17,18 The location of the P wave in relation to the QRS complex, the electrical axis of the P wave in the frontal and horizontal planes and the presence or absence of QRS alternation are the main signs used in these studies to identify

the type of reentry. The location of the P wave within the QRS complex is a specific sign of nodal reentry, but its location after the QRS complex is not the specific sign of a reentry through an accessory atrioventricular connection. <sup>14</sup> It has been suggested that the QRS alternation is a sign of reentry via an accessory atrioventricular connection, <sup>17</sup> but some investigators <sup>15,19</sup> have demonstrated that QRS alternans is a rate-related phenomenon and is independent of the tachycardia mechanism. The effects of a functional bundle branch block on the cycle length of tachycardia may help to prove the participation of an accessory atrioventricular connec-

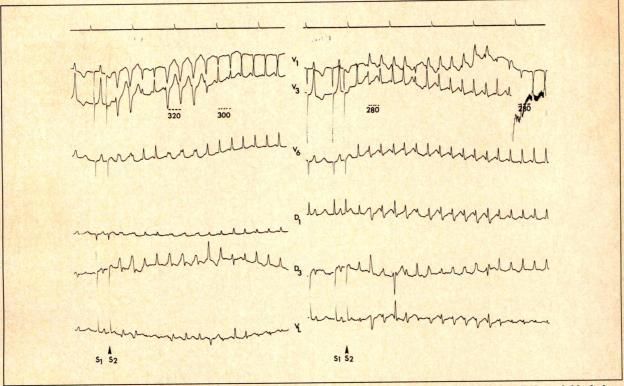


FIGURE 7. Patient 12 of group II. Induction of reciprocating tachycardia by 1 extrastimulus. The right bundle branch block does not change the cycle of tachycardia. The left bundle branch block increases the cycle of tachycardia, suggesting that the retrograde conduction uses a left-sided accessory pathway, although changes in ventriculoatrial intervals during bundle branch block were not obvious.

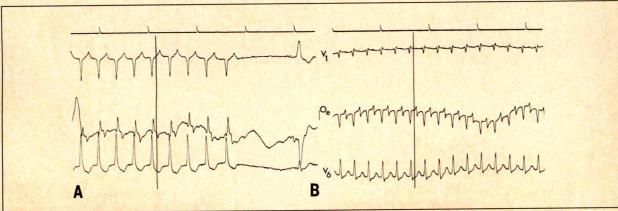


FIGURE 8. Patterns of P wave in  $V_1$  during SVT. A, esophageal electrocardiogram precedes the P wave in  $V_1$ , which was positive in this patient (7 of group II). The retrograde conduction uses a left-sided accessory atrioventricular connection. B, esophageal electrocardiogram was simultaneous with the wave in  $V_1$ , which was initially negative. In the patient (13 of group II) the retrograde conduction uses a right-sided accessory atrioventricular connection.

tion.8,13 The incidence of bundle branch block, however, was high in the study of Goldstein et al7 and is low in our study.

The study of the P wave in tachycardia may help to prove the existence of an accessory atrioventricular connection. The negativity of the P wave in lead I is a sign of reentry through a left-sided accessory atrioventricular connection<sup>13</sup> but this sign is often difficult to establish. The esophageal electrocardiogram corresponds to the left atrial activation<sup>20</sup> and in our study preceded the P wave in lead V<sub>1</sub>, which was positive in 5 patients with left-sided accessory atrioventricular connection. MacLean et al21 have reported that a positive bifid P wave in V<sub>1</sub> was recorded only with left atrial pacing and only when pacing was near the inferior pulmonary veins and coronary sinus. A negative P wave in lead V1 was recorded pacing both the left superior and right inferior atrial sites. In patients with reciprocating tachycardia using a left accessory atrioventricular connection, the P wave in lead V<sub>1</sub> was positive in 16 and indeterminate in 3.22 The P wave in V<sub>1</sub> was negative and bimodal in all but 1 patient with reciprocating tachycardia using a right bypass tract.22 The early activation of the esophageal atrial electrocardiogram compared to the occurrence of a positive P wave in V<sub>1</sub> would tend to indicate a reentry through a left-sided accessory atrioventricular connection.

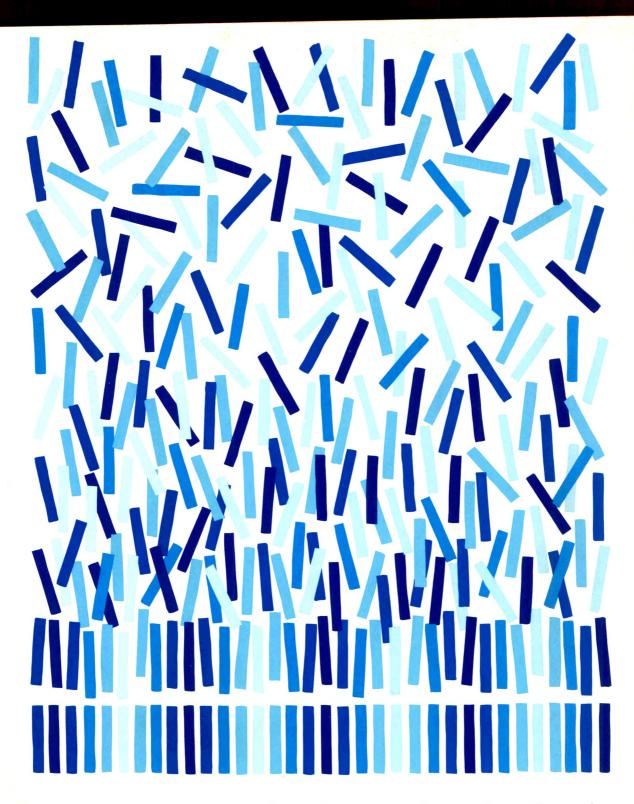
The induction of SVT required incremental atrial pacing and programmed atrial stimulation in the control state, and if necessary after the infusion of small doses of isoproterenol; with this protocol, SVT was initiated in all patients and it was possible to demonstrate its mechanism in 91% of these patients.

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<sup>1.</sup> Singh BN, et al. *American Heart J* 116 (5): 1542-1551, 1988. 2. Haffajee CI, et al. *Circ*. 80 (4): II-652, 1989. 3. Valero de Pesce EM, et al. *J. Electro* 2 (3): 215-221, 1988. 4. Dugernier TH, et al. *JAAC* 9 (2): 244A, 1987. 5. Budde TH, et al. *Eur Heart J* 8 (S2): 97, 1987.



### Safety Profile Based on 2,127 Patients Studied up to 5 Years

Cardiac: Discontinuance due to cardiac adverse effects within the first month of study: 3.6% at starting dose (450 mg); 4.9% at high dose (900 mg). Of 2,127 patients in the study, 971 had malignant arrhythmias at baseline.

**Proarrhythmia incidence 4.7%:** In 2,127 patients studied at recommended dosages in U.S. multicenter trials, proarrhythmia was manifested as ventricular tachycardia/fibrillation in 4% of the patients, and as increased PVCs in 0.7%.

Of the patients who had new or worsening VT (4%), 92% had a history of VT and/or VT/VF, 71% had coronary artery disease, and 68% had a prior myocardial infarction. The incidence of proarrhythmia in patients with less serious or benign arrhythmias (a disease state for which the drug is not indicated) which include patients with an increase in frequency of PVCs, was 1.6%. Most proarrhythmic events occurred during the first week of therapy.

**Non-Cardiac:** 1.9% or less discontinuance due to non-cardiac side effects in each of the other body systems at 450 mg/day.

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## Minimal Effect on LV Function

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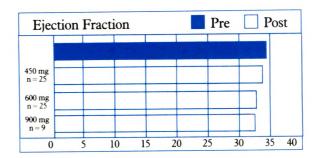
# CHF Incidence 3.7% in 2,127 Patients

Of the 3.7%:

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- 85% had CAD.
- 0.2% of patients without a prior history of CHF, attributed CHF to Rythmol.

### Clinical studies show minimal effect on LV function.\*

Study I – In 26 patients with a mean ejection fraction under 35%, no statistically significant decrease in LV ejection fraction was seen as the dose was increased from 450 mg to 900 mg from baseline.



Baker, et al, Practical Card 14: 117, 1988

Study II – In 12 patients with ejection fractions under 40%, no significant reduction of LV ejection fraction was seen as determined by nuclear ventriculography.

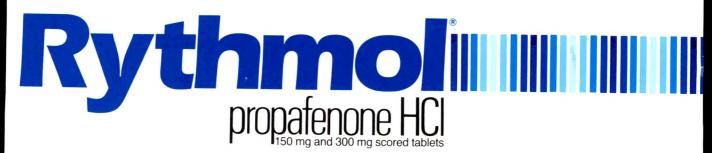
Brodsky, et al., Am Heart J;110:794-799, 1985.

Study III – 42 patients were studied by radioventriculography in control and during propafenone therapy. For the group as a whole, propafenone did not affect LVEF (47% vs 45%, p=NS).

Cueni, L; Podrid, PJ; Irnl Electrophysiology 1:6, 548-560, 1987.

\*Rythmol® exhibits both a beta blocking and a dose related negative inotropic effect. Patients with CHF should be fully compensated before Rythmol therapy is initiated.

	LVEF (%) Control Drug			
	Common			
All patients (N = 42)	47	45		
Responders ( $N = 21$ )	46	44		
Nonresponders (N = 21)	49	47		
LVEF > 50%	60	57		
LVEF < 50%	34	33		
LVEF < 30%	23	22		



### Concomitant Use Experience

With digitalis. Rythmol (propafenone HCl) produces dose related increases in serum digoxin levels. Patients on Rythmol plus digoxin therapy should have plasma levels measured. Digoxin dosage should ordinarily be reduced when Rythmol is started.

With warfarin. In patients receiving Rythmol and warfarin concomitantly, warfarin mean steady-state plasma concentrations increased 39% with corresponding increase in prothrombin times of approximately 25%. It is therefore recommended that prothrombin times be routinely monitored, and the dose of warfarin be adjusted if necessary.

With propranolol. Concomitant administration of Rythmol and propranolol has resulted in substantial increases in propranolol plasma concentration and elimination half-life with no change in propafenone plasma levels from control values. While the therapeutic range for beta blockers is wide, a reduction in dosage may be necessary during concomitant administration with Rythmol.

With calcium channel blockers. Concomitant therapy of Rythmol with diuretics and calcium channel blockers has been reported without evidence of clinically significant adverse reactions.

With cimetidine. In normal patients concomitant administration of Rythmol and cimetidine resulted in a 20% increase in steady-state plasma concentrations of Rythmol with no detectable changes in electrocardiographic parameters beyond that measured on Rythmol alone.



INDICATIONS AND USAGE

INDICATIONS AND USAGE RYTHMOL (propafenone HCI) is indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that in the judgement of the physician, are life threatening. Because of the proarrhythmic effects of RYTHMOL, its use should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks. The use of RYTHMOL is not recommended for use in patients with less severe ventricular arrhythmias, even if the patients are symptomatic. Use of RYTHMOL for the treatment of sustained ventricular tachycardia, like other antiarrhythmics, should be included in the possibil. should be initiated in the hospital.

CONTRAINDICATIONS

RYTHMOL (propafenone HCI) is contraindicated in the presence of uncontrolled congestive heart failure, cardiogenic shock, sinoatrial, atrioventricular and intraventricular disorders of impulse generation and/or conduction (e.g., sick sinus node syndrome, atrioventricular block) in the absence of an artificial pacemaker, bradycardia, marked hypotension, bronchospastic disorders, manifest electrolyte imbalance, and known hypersensitivity to the drug.

Montality: In the National Heart Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a longterm, multicenter, randomized, double blind study in patients with asymptomatic non life threatening ventricular ectopy who had a myocardial infarction more asymptomatic non life threatening ventricular ectopy who had a myocardial infarction more than six days but less than two years previously and demonstrated mild to moderate let ventricular dysfunction, an excessive mortality or nonfatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730) compared with that seen in patients assigned to carefully matched placebo treated groups (22/725). The average duration of treatment with encainide or flecainide in this study was ten months. The applicability of these results to other populations (e.g., those without recent myocardial infarction and to other antiarrhythmic drugs) is uncertain, but at present it is prudent (1) to consider any IC agent (especially one documented to provoke new serious arrhythmias) to have a similar risk and (2) to consider the risks of Class IC agents, coupled with the lack of any evidence of improved survival, generally unacceptable in patients without life threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life threatening, symptoms or signs. symptoms or signs

Proarrhythmic Effects

RYTHMOL, like other antiarrhythmic agents, may cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., tachycardia that is more sustained or more rapid which may lead to fatal consequences. It is therefore essential that each patient given RYTHMOL be evaluated electrocardiographically and clinically prior to, and during therapy to determine whether the response to RYTHMOL (propatenone HCI) supports continued treatment. Overall in clinical trials with propatenone 4.7% of all patients had new or worsened ventricular architecture. (proparenone HCl) supports continued treatment. Overall in clinical trials with propatenone, 4.7% of all patients had new or worsened ventricular arrhythmia possibly representing a proarrhythmic event (0.7% was an increase in PVCs; 4.0% a worsening, or new appearance, of VT or VF). Of the patients who had a worsening of VT (4%), 92% had a history of VT and/or VT/VF, 71% had coronary artery disease, and 68% had a prior myocardial infarction. The incidence of proarrhythmia in patients with less serious or benign arrhythmias, which include patients with an increase in frequency of PVCs, was 1.6%. Although most proarrhythmic events occurred during the first week of therapy, late events also were seen and the CAST study (see above) suggests that an increased risk is present throughout treatment

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)
PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD. IN GENERAL NOT RECEIVE
PROPAFENONE or other agents with beta adrenergic blocking activity.

Congestive Heart Failure

Congestive Heart Failure
During treatment with oral propafenone in patients with depressed baseline function (mean EF=33.5%), no significant decreases in ejection fraction were seen. In clinical trial experience, new or worsened CHF has been reported in 3.7% of patients; of those 0.9% were considered probably or definitely related to RYTHMOL. Of the patients with congestive heart failure and 85% had coronary artery disease. CHF attributable to RYTHMOL developed rarely (<0.2%) in patients who had no previous history of CHF. As RYTHMOL exerts both beta blockade and a (dose related) negative inotropic effect on cardiac muscle, patients with congestive heart failure worsens, RYTHMOL should be discontinued (unless congestive heart failure worsens, RYTHMOL should be discontinued (unless congestive heart failure worsens, RYTHMOL should be discontinued (unless congestive heart failure worsens, RYTHMOL should be discontinued (unless congestive heart failure worsens has been established.

**Conduction Disturbances** 

PRYTHMOL slows atrioventricular conduction and also causes first degree AV block. Average PR interval prolongation and increases in QRS duration are closely correlated with dosage increases and concomitant increases in propafenone plasma concentrations. The incidence of first degree, second degree, and third degree AV block observed in 2,127 patients was 2.5%, 0.6%, and 0.2%, respectively. Development of second or third degree AV block requires a reduction in dosage or discontinuation of RYTHMOL. Bundle branch block (1.2%) and interventionally conduction default of 12%, have been reported in patients required. and intraventricular conduction delay (1.1%) have been reported in patients receiving propafenone. Bradycardia has also been reported (1.5%). Experience in patients with sick sinus node syndrome is limited and these patients should not be treated with propafenone.

Effects on Pacemaker Threshold

RYTHMOL may alter both pacing and sensing thresholds of artificial pacemakers. Pacemakers should be monitored and programmed accordingly during therapy.

Hematologic Disturbances

Hematologic Disturbances
One case of agranulocytosis with fever and sepsis, probably related to use of propatenone, was seen in U.S. clinical trials. The agranulocytosis appeared after 8 weeks of therapy. Propatenone therapy was stopped and the white count had normalized by 14 days. The patient recovered. In the course of over 800.000 patient years of exposure during marketing outside the U.S. since 1978, seven additional cases have been reported. In one of these, concomitant captopril, a drug known to cause agranulocytosis, was used. Unexplained fever and/or decrease in white cell count, particularly during the first three months of therapy, warrant consideration of possible agranulocytosis/granulocytopenia. Patients should be instructed to promptly report the development of any signs of infection such as fever, sore throat or chills.

PRECAUTIONS

Propate Dystinction:

Propate none is highly metabolized by the liver and should, therefore, be administered cautiously to patients with impaired hepatic function. The dose of propatenone given to patients with impaired hepatic function should be significantly reduced. Careful monitoring for excessive pharmacological effects (see OVERDOSAGE) should be carried out. Renal Dysfunction:

A considerable percentage of propatenone metabolites (18.5%-38% of the dose/48 hours) are excreted in the urine. Until further data are available, RYTHMOL should be administered

monitored for signs of overdosage (see OVERDOSAGE) Elevated ANA Titers: cautiously to patients with impaired renal function. These patients should be carefully

Positive ANA titers have been reported in patients receiving propafenone. Patients who develop an abnormal ANA test should be carefully evaluated and, if persistent or worsening elevation of ANA titers is detected, consideration should be given to discontinuing therapy.

Impaired Spermatogenesis:

Impaired Spermatogenesis:

Reversible disorders of spermatogenesis have been demonstrated in monkeys, dogs and rabbits after high dose intravenous administration. Evaluation of the effects of short term propafenone administration on spermatogenesis in 11 normal subjects suggests that propafenone produced a reversible, short term drop (within normal range) in sperm count. Subsequent evaluations in 11 patients receiving propafenone chronically have suggested no

effect of propatenone on sperm count

effect of propafenone on sperm count.

Drug Interactions: Quinidine: Small doses of quinidine completely inhibit the hydroxylation metabolic pathway, making all patients, in effect, slow metabolizers. There is, as yet, too little information to recommend concomitant use of propafenone and quinidine. Local Anesthetics: Concomitant use of local anesthetics may increase the risks of central nervous system side effects. Digitalis: RYTHMOL produces dose related increases in serum digoxin levels ranging from about 35% at 450 mg/day to 85% at 900 mg/day propafenone without affecting digoxin renal clearance. Digoxin dosage should ordinarily be reduced when propafenone is started. Beta-Antagonists: Propafenone appears to inhibit the hydroxylation pathway for propranolol and metoprolol (just as quinidine inhibits propafenone metabolism). While the therapeutic range for beta-blockers is wide, a reduction in dosage may be necessary during concomitant administration with propafenone. Warfarin: In a study of eight healthy subjects receiving propafenone and warfarin concomitantly, mean steady-state warfarin plasma concentrations increased 39% with a corresponding increase in warfarin plasma concentrations increased 39% with a corresponding increase in prothrombin times of approximately 25%. It is therefore recommended that prothrombin times be routinely monitored and the dose of warfarin be adjusted if necessary. Cimetidine: Concomitant administration of propafenone and cimetidine in 12 healthy subjects resulted in a 20% increase in steady-state plasma concentrations of propafenone with no detectable changes in electrocardiographic parameters beyond that measured on propafenone alone.

changes in electrocardiographic parameters beyond that measured on propadenone alone. Other: Limited experience with propadenone combined with calcium antagonists and diuretics has been reported without evidence of clinically significant adverse reactions. Carcinogenesis, Mutagenesis, Impairment of Fertility: Life time maximally tolerated oral dose studies in mice (up to 360 mg/kg/day) and rats (up to 270 mg/kg/day) provided no evidence of a carcinogenic potential for propadenone. RYTHMOL was not mutagenic when assayed for genotoxicity. Pregnancy Teratogenic Effects: Pregnancy Category C.: Propadenone has been shown to be embryotoxic in rabbits and rats when given in doses 10 and 40 times, respectively, the maximum recommended human dose. No teratogenic potential was apparent in either species. There are no adequate and well controlled studies in pregnant women. Propadenone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pregnancy Nonteratogenic Effects: In a perinatal and postnatal study in rats, propadenone, at dose levels of 6 or more times the maximum recommended human dose, produced dose dependent increases in maternal and neonatal mortality, decreased maternal and pup body weight gain and reduced neonatal physiological recommended numan dose, produced dose dependent increases in maternal and rednated mortality, decreased maternal and pup body weight gain and reduced neonatal physiological development. Labor and Delivery: It is not known whether the use of propafenone during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetrical intervention. Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from RYTHMOL, a decision should be made whether to discontinuation of the importance of the discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and efficacy of RYTHMOL in children has not been established. Geriatric Use: There do not appear to be any age-related differences in adverse reaction rates in the most commonly reported adverse reactions. Because of the possible increased risk of impaired hepatic or renal function in this age group, RYTHMOL should be used with caution. The effective dose may be lower in these patients. ADVERSE REACTIONS

ADVERSE REACTIONS

Adverse reactions associated with RYTHMOL (propafenone HCl) occur most frequently in the gastrointestinal, cardiovascular, and central nervous systems. About 20% of patients discontinued due to adverse reactions.

Adverse reactions reported for ≥1% of 2.127 patients who received propafenone in U.S. clinical trials are presented in the following list. Dizziness, Nausea and/or Vomiting, Unusual Taste, Constipation, Fatigue, Dyspepsia, Palpitations, Rash, First Degree AV Block, Diarrhea, Weakness, Dry Mouth, Syncope/Near Syncope, Increased QRS Duration, Chest Pain, Anorexia, Abdominal Pain/Cramps, Ataxia, Insomnia, Premature Ventricular Contraction(s), Bradycardia, Anxiety, Edema, Tremor(s), Diaphoresis, Bundle Branch Block, Drowsiness, Atrial Fibrillation, Flatulence, Hypotension, Intraventricular Conduction Delay, Joint(s) Pain. na addition, the following adverse reactions were reported less frequently than 1% either in Artial Fibrillation, fieldlerice, Appoteinson, intavenificual colination belay, somis) Fam. In addition, the following adverse reactions were reported less frequently than 1% either in clinical trials or in marketing experience (adverse events for marketing experience are given in italics). Causality and relationship to propatenone therapy can not necessarily be judged from these events. Cardiovascular System: Atrial flutter, AV dissociation, cardiac arrest, flushing, hot flashes, sick sinus syndrome, sinus pause or arrest, supraventricular tachycardia. Nervous System: Abnormal dreams, abnormal speech, abnormal vision, apnea, come confluence developed properties of developed properties of the properties o tachycardia. **Nervous System**: Abnormal dreams, abnormal speech, abnormal vision, *apnea*, *coma*, confusion, depression, memory loss, numbness, paresthesias, psychosis/mania, seizures (0.3%), tinnitus, unusual smell sensation, vertigo. **Gastrointestina**: A number of patients with liver abnormalities associated with propafenone therapy have been reported in foreign postmarketing experience. Some appeared due to hepatocellular injury, some were cholestatic and some showed a mixed picture. Some of these reports were simply discovered through clinical chemistries, others because of clinical symptoms. One case was rechallenged with a positive outcome. Cholestasis (0.1%), elevated liver enzymes (alkaline phosphatase, serum transaminases) (0.2%), gastroenteritis, hepatitis (0.03%) **Hematologic**. Agranulocytosis, anemia, bruising, granulocytopenia, *increased bleeding time*, leukopenia, purpura, thrombocytopenia. **Other**: Alopecia, eye irritation, *hyponatremia/inappropriate ADH secretion*, imporence, increased glucose, *kidney failure*, positive ANA (0.7%), *lupus erythematosis*, muscle cramps, muscle weakness, nephrotic syndrome, pain, pruritus. rythematosis, muscle cramps, muscle weakness, nephrotic syndrome, pain, pruritus

The symptoms of overdosage, which are usually most severe within 3 hours of ingestion may include hypotension, somnolence, bradycardia, intraatrial and intraventricular conduction disturbances, and rarely convulsions and high grade ventricular arrhythmias. Defibrillation as well as infusion of dopamine and isoproterenol have been effective in controlling rhythm and blood pressure. Convulsions have been alleviated with intravenous diazepam. General supportive measures such as mechanical respiratory assistance and external cardiac massage may be necessary.

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# Effective Antiarrhythmic Therapy with a Unique Pharmacologic Profile

**Excellent V-Tach efficacy:** Rythmol provided effective suppression of VT beats in patients with either sustained or non-sustained VT.

**Safety Profile:** 3.6% discontinuance due to cardiac and 1.9% or less discontinuance due to non-cardiac side effects at 450 mg/day (N = 1430).

**Beta Blocker Activity:** equal to 1/40th of propranolol. Patients with bronchospastic disease should, in general, not receive propafenone.

Available in 150 mg and 300 mg scored tablets.

Rythmol 150mg
Rythmol 150mg
#100
Sig. 1 tablet
Sig. 7.1.D.

#### **Recommended Dosage**



Begin therapy with <u>Rythmol</u> 150 mg t.i.d. (450 mg/day)



Increase to 225 mg t.i.d. (incremental increases can be implemented after 3 or 4 days) (675 mg/day)

If necessary increase to 300 mg t.i.d. (Maximum recommended dose 900 mg per day)



## Comparison of Long-Term Hemodynamic Effects at Rest and During Exercise of Lisinopril Plus Sodium Restriction Versus Hydrochlorothiazide in Essential Hypertension

Per Omvik, MD, and Per Lund-Johansen, MD

To investigate whether sodium restriction might replace thiazides in promoting blood pressure (BP) reduction by angiotensin-converting enzyme inhibitors, the long-term hemodynamic effect of lisinopril plus sodium restriction versus lisinopril plus hydrochlorothiazide was compared at rest and during dynamic exercise in 2 groups of essential hypertensive patients. Mean pretreatment intraarterial BP at rest sitting was 177/107 mm Hg. The patients were randomly allocated to lisinopril combined with either low salt diet (low salt group, n = 13) or hydrochlorothiazide (diuretic group, n = 12). After 1 year of treatment the mean dose of lisinopril was 25 mg in both groups. In the low salt group sodium excretion was reduced from 188 to 129 mmol/24 hours (p <0.01). In the diuretic group sodium excretion was unchanged with a mean dose of hydrochlorothiazide of 19 mg. BP was reduced (p <0.001) in both groups: at rest 16 and 21% and during exercise 10 and 13% in the low salt and the diuretic groups, respectively. Total peripheral resistance was reduced (p < 0.05) in both groups: at rest 14 and 7% and during exercise 8 and 5% in the low salt and the diuretic groups, respectively. Overall cardiac output was reduced (p <0.05) in the diuretic group but remained unchanged in the low salt group. Thus, lisinopril—either in combination with a diuretic or sodium restriction—induces marked reduction in BP due to decreases in peripheral vascular resistance both at rest and during exercise. Lisinopril plus low salt diet reduces the risk of unwanted metabolic effects and leads to more complete hemodynamic normalization than lisinopril plus a diuretic and should be preferred when this leads to satisfactory BP control.

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odium restriction and diuretic treatment activate the renin-angiotensin system both in normotensive subjects<sup>1,2</sup> and in essential hypertensive patients.<sup>1,3</sup> Under these conditions the blood pressure (BP) becomes more dependent on either circulating<sup>4-7</sup> or locally produced<sup>8,9</sup> angiotensin II. Although drugs that impair the conversion of angiotensin I to angiotensin II—the angiotensin-converting enzyme inhibitors—may control high BP in low renin as well as high renin hypertension, <sup>10,11</sup> these compounds reduce BP more effectively after salt and volume depletion.<sup>12,13</sup> Therefore, to enhance the antihypertensive effect, a thiazide diuretic has often been added in clinical trials of converting enzyme inhibitors.<sup>12-15</sup>

The use of thiazide diuretics is associated with unwanted metabolic effects. 16,17 To reduce these and to avoid multiple drug regimens, we investigated whether sodium restriction might replace a thiazide to potentiate the antihypertensive effect of converting enzyme inhibition in essential hypertensive patients, by comparing the hemodynamic effects of lisinopril either in combination with moderate sodium restriction or hydrochlorothiazide.

During physical exercise BP is increased by stimulation of the sympathetic nervous system. 19,20 Thus, it has been suggested that converting enzyme inhibitors might lower BP less during exercise than rest. 21 The hemodynamic measurements were therefore performed at rest and at 3 levels of steady state bicycle exercise.

#### **METHODS**

Patients: The study protocol was approved by the Norwegian State Drug Control and the Regional Ethical Committee. All patients gave informed consent to participate in the study. Twenty-five actively working men aged 33 to 68 (mean  $51 \pm 9$ ) years with mild or moderate hypertension (World Health Organization stage I or II) were recruited from the Hypertension Outpatient Clinic, Medical Department A, of the Haukeland Hospital in Bergen. Diastolic BP ranged between 100 and 120 mm Hg on at least 3 outpatient visits before the patients entered the study. Secondary hypertension was ruled out by conventional laboratory tests. The mean body weight was  $84.8 \pm 11.0$  kg, height  $1.80 \pm 0.05$  m and body surface area  $2.03 \pm 0.13$  m<sup>2</sup>.

Hemodynamics: Hemodynamic measurements were performed at rest supine and sitting and during steady state (after 6 to 8 minutes) bicycle exercise at 50, 100,

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From the Medical Department, Section of Cardiology, Haukeland Hospital, 5021 Bergen, Norway. Lisinopril and hydrochlorothiazide for this study were provided by Merck Sharp and Dohme, Norge, A/S. Manuscript received June 26, 1989; revised manuscript received October 2, 1989, and accepted October 4.

TABLE I Hemodynamic Effects of Lisinopril Plus Sodium Restriction at Rest and During Exercise in Essential Hypertension in 13

	Rest Sup	ine	Rest Sitti	ng	50 Watts		100 Watts		150 Watts	5 74 18 75
	В	А	В	A	В	A	В	Α	В	A
VO <sub>2</sub> (min <sup>-1</sup> m <sup>-2</sup> )			167	161	587	598	872	899	1,257	1,272
SD			25	14	43	131	102	127	131	202
Change (%)			A MARKET HE	-4		2		3		1
HR (beats/min)	67	66	72	71	104	101	129	127	157	154
SD	10	12	13	13	10	13	18	15	15	18
Change (%)	Metal Proper	-2		-2		-3	-		_	
SI (ml stroke <sup>-1</sup> m <sup>-2</sup> )	44	44	34	35	48	50	50	51	49	49
SD	6	6	4	6	5	4	2	5	10	10
Change (%)		0		3		3		2		0
CI (liters/min m <sup>-2</sup> )	3.0	2.9	2.5	2.5	5.0	5.0	6.3	6.4	7.5	7.4
SD	0.5	0.6	0.5	0.5	0.6	0.6	0.8	0.7	1.3	0.9
Change (%)		-3		0		0		2		
SAP (mm Hg)	158	134	171	147	190	172	198	184	218	204
SD	10	15	12	18	10	16	15	18	23	26
Change (%)		15 <sup>‡</sup>		14 <sup>‡</sup>		10 <sup>‡</sup>	<u> -</u>	7‡		6*
DAP (mm Hg)	95	78	103	88	104	92	108	95	117	107
SD	5	8	7	10	7	9	9	9	13	14
Change (%)		18 <sup>‡</sup>		15 <sup>‡</sup>	-	12‡	-1	2‡		9‡
MAP (mm Hg)	118	99	129	110	139	123	144	128	159	144
SD	5	10	6	12	8	13	11	12	18	21
Change (%)		17‡	-	15 <sup>‡</sup>	_	12 <sup>‡</sup>	-1	1‡	_	9†
TPRI (dynes s cm <sup>-5</sup> m <sup>2</sup> )		2,837	4,347	3,741	2,262	2,067	1,854	1,664	1,757	1,649
SD	611	552	806	742	311	351	308	229	486	345
Change (%)	+	14		14		-9	-10	0	-6	

p <0.05; † p <0.01; ‡ p <0.001 = after: B = before 1 year of tre

A = after; B = before 1 year of treatment; CI = cardiac index; DAP = diastolic arterial pressure; HR = heart rate; MAP = mean arterial pressure; SAP = systolic arterial pressure; SD standard deviation; SI = stroke index; TPRI = total peripheral resistance index; VO<sub>2</sub> = oxygen consumption.

and 150 watts. All patients were able to bicycle at the 3 work levels, but because of exertion 2 patients did not complete the highest level. The measurements were made on an outpatient basis between 9 and 12 A.M. in a quiet laboratory after a light breakfast (1 glass of juice and 2 slices of bread). Intraarterial pressure was measured continuously through a thin (0.9 mm) polyethylene catheter in the brachial artery. The mean arterial pressure was obtained by electrical damping of the pressure curve. An average of 40 cardiac cycles was used for each pressure measurement. Heart rate was recorded on the electrocardiogram. Cardiac output was measured in duplicate by Cardiogreen® and oxygen consumption was measured by the Douglas bag technique. Beckman gas analyzers were used for oxygen and carbon dioxide measurements. Cardiac index, stroke index and total peripheral resistance index were calculated by conventional formulas. The hemodynamic methods have been described in more detail elsewhere. 22 As shown previously, the long-term reproducibility of these methods is high.<sup>23</sup>

Extracellular fluid volume was measured by radiosulfate dilution and plasma volume by iodinated human serum albumin. Blood volume was calculated from plasma volume and central venous blood packed cell volume. The interstitial fluid volume was calculated as extracellular fluid volume minus plasma volume. Sodium, potassium, creatinine and urate concentrations of plasma and urine samples were determined by standard laboratory methods.

Protocol: After the first hemodynamic study the patients were randomly allocated to 2 groups receiving either lisinopril plus moderate low salt diet (low salt group) or lisinopril plus hydrochlorothiazide (diuretic group). Lisinopril was administered in an initial dose of 20 mg daily, increasing to 40 mg daily after 2 weeks if the treatment goal (sitting BP ≤140/90 mm Hg) had not been reached.

The 13 patients in the low salt group were instructed to reduce daily sodium intake by decreasing table salt, avoiding salt in cooking and also avoiding canned and presalted foods. This was calculated to lower daily sodium intake to approximately 120 mmol. The 12 patients in the diuretic group were given 12.5 to 25 mg hydrochlorothiazide daily in addition to lisinopril. No dietary changes were recommended for these patients. All patients were then seen in the outpatient clinic at 4- to 8week intervals for BP measurements and quantitation of daily sodium intake by measurements of 24-hour sodium excretion. Creatinine excretion was used to evaluate the completeness of urine samples.

After a treatment period of 8 to 16 (mean 11) months, the hemodynamic study was repeated. The patients took the regular morning dose at 7 A.M. and the hemodynamic measurements were performed between 9 and 12 A.M.

Statistics: Results are presented as mean ±1 standard deviation for each group. Within groups the statistical significance of differences was tested by the Student t test for paired samples. Between groups the differences were tested by analysis of variance.

#### RESULTS

At the first hemodynamic study all subjects had an increased total peripheral resistance index, at rest sitting

averaging 4,372 dynes s cm<sup>-5</sup> m<sup>2</sup>. The mean intraarterial pressure was 177/107 mm Hg, cardiac index 2.50 liters/min m<sup>2</sup> and heart rate 72 beats/min. The control BP tended to be higher in the diuretic than in the low salt group but this difference was not statistically significant (Tables I and II).

Casual blood pressure and side effects: Casual systolic BP at rest sitting was reduced by ≥20 mm Hg, and diastolic BP by ≥15 mm Hg, in all but 2 patients in each group. In the low salt group the BP was reduced from an average of 169/106 mm Hg after the control period to 138/85 mm Hg (p <0.001) after 1 year of active treatment (Figure 1). In the diuretic group the BP was reduced from 180/110 to 134/87 mm Hg (p <0.001). The mean daily dose of lisinopril was 25 mg in both groups and the mean dose of hydrochlorothiazide in the diuretic group was 19 mg. There were no serious side effects. Three patients reported mild dizziness and 2 had dry coughs. Two patients (1 in each group) complained about impotence but after dose reduction (lisinopril for the patient in the low salt group and hydrochlorothiazide for the patient in the diuretic group) the problem disappeared. All 25 patients completed the study.

Hemodynamics: The main results are shown in Figures 2 and 3 and Tables I and II. There were no significant changes in oxygen consumption after treatment.

Low salt group: Overall the intraarterial systolic and diastolic pressures were reduced by 14 to 18% at rest and by 6 to 12% during exercise, respectively. In 11 patients (85%) the intraarterial pressure at rest sitting was reduced to <160/95 mm Hg and in 3 patients (23%) to <140/90 mm Hg (Figure 4).

The heart rate decreased slightly, on average by 1 to 3 beats/min in the different situations, but these changes were not statistically significant. The stroke index and the cardiac index also remained virtually unchanged, varying by <4% from the first to the second study.

Total peripheral resistance index was reduced in all but 1 patient. On average the reduction was 14% at rest and between 6 and 10% during exercise (F = 15.5; p <0.001).

Diuretic group: The mean intraarterial pressure was reduced in all situations. At rest sitting the intraarterial pressure was reduced to <160/95 mm Hg in 9 patients (75%) and to <140/90 mm Hg in 6 (50%) (Figure 4). The mean BP reduction was 21 to 23% at rest and 9 to 18% during exercise.

The heart rate was reduced by an average of 3 to 7 beats/min in the different situations (statistically significant in the rest supine and sitting positions only). A small but insignificant reduction was observed in stroke index, on average ranging between 1 and 3 ml/stroke/ m<sup>2</sup> in the different situations. Also, cardiac index was slightly reduced but only attained statistical significance (p <0.01) in the rest supine and sitting positions. By analysis of variance an overall reduction of cardiac index was demonstrated (F = 9.5; p < 0.05).

The total peripheral resistance index was reduced in all but 3 patients at rest and all but 2 during exercise. The mean reduction (F = 4.3; p < 0.05) was 6 to 8% at rest sitting and supine, and 3 to 9% at the different exercise levels, respectively.

Comparison of hemodynamic changes in the low salt and diuretic groups: Although the pretreatment BP of the diuretic group tended to be higher than in the low salt group (Figure 5), the BPs in the 2 groups were almost identical at the second hemodynamic study. Hence, the reduction of intraarterial pressure was greater in the former group (F >4.3; p < 0.05) (Figure 6).

The responses of cardiac index were statistically significantly different between the 2 groups: while cardiac index in the low salt group remained unchanged after 1 year it was reduced by 5 to 16% (F = 15.8; p < 0.001) in the diuretic group (Figure 6).

The overall changes in heart rate and stroke index after treatment were also statistically significantly different in the 2 groups (F >5.8; p <0.05).

The mean reduction of total peripheral resistance index tended to be greater both at rest and during exercise in the low salt than in the diuretic group, but these differences were not statistically significant.

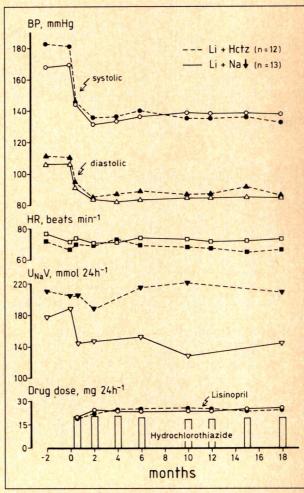


FIGURE 1. Effect of lisinopril (Li) plus low salt diet (low salt group; circles) or hydrochlorothiazide (diuretic group; triangles) on casual blood pressure (BP), heart rate (HR) and daily sodium excretion (U<sub>Na</sub>V) in essential hypertensive patients. Mean dose of lisinopril is shown for both groups. Bars indicate mean daily dose of hydrochlorothiazide in the diuretic group. Measurements were made in control period and during 18 months of therapy.

TABLE II Hemodynamic Effects of Lisinopril Plus Hydrochlorothiazide at Rest and During Exercise in Essential Hypertension in 12 **Patients** 

	Rest Supine		Rest Sitti	ng	50 Watts		100 Watts		150 Watt (n = 10)	150 Watts (n = 10)	
	В	Α	В	Α	В	Α	В	Α	В	Α	
VO <sub>2</sub> (min <sup>-1</sup> m <sup>-2</sup> )			164	164	597	603	907	873	1,405	1,472	
SD			26	25	80	60	112	155	150	144	
Change (%)				0		1		-4		5	
HR (beats/min)	65	60	71	64	103	97	129	124	153	150	
SD	11	9	13	9	14	12	16	18	14	16	
Change (%)		-8*	_	10*	1	-6		-4		-2	
SI (ml stroke <sup>-1</sup> m <sup>-2</sup> )	48	45	36	35	54	52	54	52	56	54	
SD	8	9	7	7	8	8	8	9	7	8	
Change (%)		-6		-3		-4		-4		-4	
CI (liters/min m <sup>-2</sup> )	3.1	2.6	2.6	2.2	5.4	5.0	6.9	6.4	8.3	7.9	
SD	0.5	0.3	0.4	0.2	0.7	0.7	0.9	0.9	0.9	0.1	
Change (%)	-	16 <sup>†</sup>		15 <sup>†</sup>		-7		-7		-5	
SAP (mm Hg)	172	132	184	144	205	173	217	189	221	198	
SD	21	23	22	22	32	34	39	38	19	30	
Change (%)		23 <sup>‡</sup>	<u>_</u>	22‡		16 <sup>‡</sup>	-1	3 <sup>‡</sup>		10 <sup>‡</sup>	
DAP (mm Hg)	100	78	112	88	114	93	116	100	118	107	
SD	7	13	8	11	15	14	19	18	7	17	
Change (%)	-	22‡	-	21‡	- 1	18 <sup>†</sup>	-1	4†		9*	
MAP (mm Hg)	126	98	137	112	152	124	156	134	159	144	
SD	12	16	11	17	21	22	27	25	13	23	
Change (%)		22 <sup>‡</sup>	-	18‡		18 <sup>‡</sup>	-1	4†		.gt	
TPRI (dynes s cm <sup>-5</sup> m <sup>2</sup> )	3,387	3,121	4,399	4,126	2,269	2,068	1,837	1,765	1,531	1,487	
SD	685	743	773	938	427	431	428	460	202	349	
Change (%)	SENTEN SE	-8		-6		-9		4		3	

Abbreviations as in Table I.

	BWT	PV	BV	ECF	PV/IF
	(kg)	(ml)	(ml)	(liters)	Ratio
Lisinopril + sodium re	estriction (n = 13)				TO THE REAL PROPERTY.
Control	88.0 ± 13.7	3,793 ± 750	$6,095 \pm 1,068$	13.9 ± 2.5	$0.38 \pm 0.06$
Treatment	86.7 ± 13.2	$3,692 \pm 720$	$5,890 \pm 1,056$	13.3 ± 2.6	$0.39 \pm 0.06$
Change (%)	-2	-2	-3	-5	
Lisinopril + diuretic (r	1 = 12)				
Control	$81.4 \pm 5.8$	3,974 ± 469	$6.297 \pm 770$	13.7 ± 2.8	$0.42 \pm 0.07$
Treatment	$80.0 \pm 6.9$	3,828 ± 721	5,998 ± 1,305	12.6±1.7	$0.44 \pm 0.13$
Change (%)	-2	-4	-5	-8*	2.7720.10

\* p <0.05. BWT = body weight; BV = blood volume; ECF = extracellular fluid volume; IF = interstitial fluid volume; PV = plasma volume. Values are mean  $\pm$  standard deviation.

	Plasma Concentration		Electrolyte Excretion				
	Na (mmol/liters)	K (mmol/liters)	Na (mmol/24 hours)	K (mmol/24 hours)	Na/K Ratio		
Lisinopril + sodium	restriction (n = 13)						
Control	$141.2 \pm 2.4$	$4.13 \pm 0.27$	188 ± 66	78 ± 26	$2.41 \pm 1.31$		
Treatment	$138.8 \pm 2.8$	$4.23 \pm 0.23$	129 ± 51	84 ± 29	$1.54 \pm 0.39$		
Change (%)	-2	2	<b>−3</b> 1†	7	-0.87 <sup>‡</sup> (ratio)		
Lisinopril + diuretic	c (n = 12)				(1410)		
Control	142.6 ±2.9	$4.09 \pm 0.38$	205 ± 33	$74 \pm 30$	2.73±0.69		
Treatment	139.2 ± 3.2	4.04 ±0.24	$220 \pm 56$	92 ± 29	2.39±0.83		
Change (%)	2*	-1	7	24	-0.34 (ratio)		

Values are mean ± standard deviation.

Body weight, body fluid volumes and electrolyte excretion: Before treatment no significant differences were observed in body weight, body fluid volumes (Table III) or electrolyte excretion between the 2 groups (Table IV). After 1 year there were slight, insignificant reductions in body weight, plasma volume and blood volume in both groups. In the diuretic group the extracellular fluid volume was reduced by 1.1 liter (8%; p <0.05). In this group both sodium and potassium excretion at the second hemodynamic study were unchanged (Table IV) whereas in the low salt group the sodium excretion was reduced by an average of 59 mmol/day (32%; p <0.01). Although individual data showed variation of sodium excretion during the trial, the mean sodium excretion was well below control throughout the treatment period (Figure 1). In the low salt group the urinary sodium/potassium ratio was reduced (p <0.001) while it was unchanged in the diuretic group. Plasma potassium concentration tended to be lower in the diuretic group (4.04 vs 4.23 mmol/liters, difference not significant) while the urate concentration was higher (374 vs 339 μmol/liters; p <0.01). Except for a small reduction of serum sodium concentration (143 to 139 mmol/liters; p <0.01) in the diuretic group, no significant changes occurred in serum concentrations of electrolytes or creatinine in any of the groups.

# DISCUSSION

This study showed that long-term treatment with lisinopril, both in combination with a low salt diet or hydrochlorothiazide, effectively reduced BP at rest as well as during exercise in patients with essential hypertension. The BP reduction was in the same order of magnitude as seen with other converting enzyme inhibitors. 12-15,24,25 By both treatment combinations, the BP lowering after lisinopril was associated with reduction of total peripheral resistance index. However, total peripheral resistance was still higher than in normotensive subjects of similar age. 22 The combination of lisinopril and diuretic also induced a small reduction in cardiac index. In the diuretic group plasma potassium concentration tended to decrease while urate concentration increased. The number of side effects were few, and no patient had to discontinue medication due to adverse effects.

Blood pressure: The combination of lisinopril and moderate low salt diet adequately controlled the BP in about half the patients in the low salt group. However, the combination of lisinopril and hydrochlorothiazide reduced BP more effectively than lisinopril plus low salt diet (at rest 21 vs 16%). Although this difference is of doubtful clinical significance, the greater reduction in BP with lisinopril plus hydrochlorothiazide suggests that some patients not responding adequately to the combination of a converting enzyme inhibitor plus low salt diet might achieve better BP control in combination with a diuretic. To clarify this question further studies are required. However, since a diuretic implies risk of metabolic side effects, lisinopril plus low salt diet should be preferred when this leads to satisfactory BP control.

Sodium and volume depletion by low salt diet and diuretic treatment stimulate renin production and activate angiotensin II.<sup>1-3</sup> Under these conditions the BP

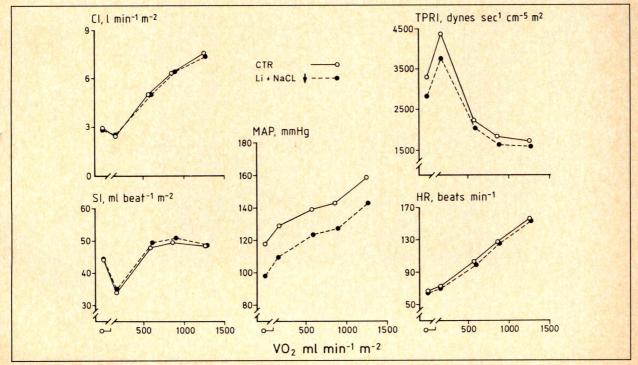


FIGURE 2. Hemodynamic effects of lisinopril plus low salt diet in 13 essential hypertension patients at rest and during exercise. Cardiac index (CI), stroke index (SI), mean arterial pressure (MAP), total peripheral resistance index (TPRI) and heart rate (HR) in relation to oxygen consumption (VO<sub>2</sub>) at rest supine and sitting and during 3 levels (50, 100 and 150 watts) of steady-state bicycle exercise are shown. VO<sub>2</sub> was only measured at rest sitting and during exercise. Open circles indicate measurements before and closed circles after 1 year of treatment. Values are means.

control becomes more dependent on the renin-angiotensin system. Hence, inhibition of this hormonal axis—either by angiotensin II analog, 26 converting enzyme inhibitors 12-15 or renin antibodies 27—reduces BP more effectively after contraction of body fluid volumes. In the

present study the fluid volumes, in particular the extracellular fluid volume, were reduced more impressively after diuretic treatment than after reduction in salt ingestion. The tendency for greater BP reduction when lisinopril was combined with a diuretic than with a low

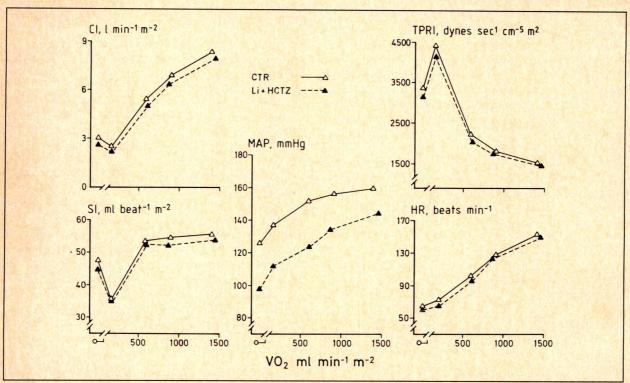


FIGURE 3. Hemodynamic effects of lisinopril plus hydrochlorothiazide in 12 essential hypertension patients at rest and during exercise. Abbreviations as in Figure 2.

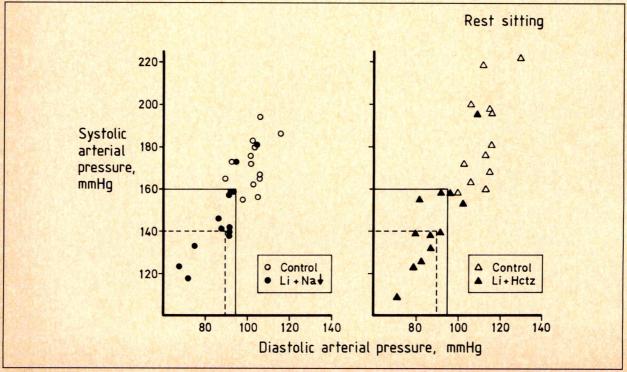
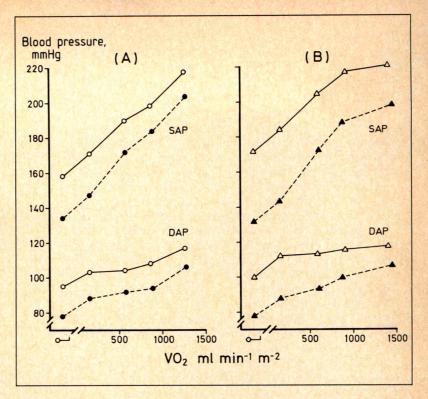


FIGURE 4. Intraarterial systolic and diastolic pressures before (open circles) and after (closed circles) 1 year of treatment with lisinopril plus low sodium diet (left) or hydrochlorothiazide (right) in essential hypertension. Rectangles show pressure limits of borderline hypertension (160/95 mm Hg) and normotension (140/90 mm Hg). Hctz = hydrochlorothiazide; Li = lisinopril.

FIGURE 5. Comparison of blood pressure responses to exercise before and after lisinopril plus low sodium diet (A) or hydrochlorothiazide (B) in essential hypertensive patients. Open circles indicate measurements before and closed circles after 1 year of treatment. DAP = diastolic arterial pressure; SAP = systolic arterial pressure; VO<sub>2</sub> = oxygen consumption. Values are means.



salt diet could, therefore, partly be due to greater reduction of body fluid volume. As suggested for captopril, an alternative mechanism could be late resistance to lisinopril. A direct effect of thiazide diuretics on the arterioles has been suggested as a mechanism of their hypotensive effect, 3,28 but no additional decrease in total peripheral resistance index seemed to occur in this study (Figure 3).

The reduction of sodium intake in this study was small. However, this reduction in sodium intake is in agreement with our previous experience of what can be achieved on a long-term basis with low salt diet in patients with mild essential hypertension.<sup>29</sup> When used as a monotherapy for hypertension, moderate sodium restriction induced only a slight reduction in BP, and the total peripheral resistance index was not reduced. In the present study the combination of low salt diet and lisin-opril markedly reduced total peripheral resistance.

Central hemodynamics: Total peripheral resistance index, which before treatment was markedly increased above normal, 22 was reduced by both regimens. The normalization of central hemodynamics was more complete with lisinopril plus low salt diet than lisinopril plus hydrochlorothiazide, with greater reduction of total peripheral resistance index and no change in cardiac index. However, these hemodynamic differences are minor and their clinical significance unknown.

In the group receiving lisinopril plus hydrochlorothiazide, a significant reduction was seen in cardiac index (Figure 6). Thus, from a hemodynamic point of view the greater reduction of BP in this group can best be explained by an additional effect on cardiac index. One possible mechanism for the decrease in cardiac index in the diuretic group is the greater body fluid volume contraction. A similar relation has previously been described after treatment with captopril.<sup>24</sup> From experi-

mental and clinical studies it is well known that converting enzyme inhibitors are potent venodilators. Hence, by 2 mechanisms—decrease in body fluid volume and peripheral venous pooling—converting enzyme inhibi-

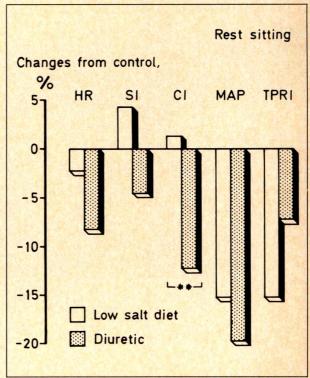


FIGURE 6. Hemodynamic effects of lisinopril plus low sodium diet (group 1; open bars) or hydrochlorothiazide (group 2; stippled bars) in essential hypertension. The figure shows percent changes from control. \*\* indicates significant difference between groups (p <0.01). Values are means. Abbreviations as in Figure 2.

tors and hydrochlorothiazide can reduce preload and thereby cardiac output.

In the group receiving a diuretic in addition to lisinopril a small reduction in heart rate, as well as in stroke index, contributed to the reduction in cardiac index. Similar heart rate responses have previously been reported from other studies on converting enzyme inhibitors. 6,10,12,15,24,25,30 Only after the first dose of a converting enzyme inhibitor has a modest initial reflex tachycardia been described. 10,31 It is thought that the lack of tachycardia after converting enzyme inhibition in spite of peripheral vasodilatation is due to parasympathetic stimulation. 10,12,32 Because both converting enzyme inhibitors<sup>33,34</sup> and thiazides<sup>35</sup> may interfere with sympathetic tone and reactivity to noradrenaline, the small reduction in heart rate and stroke index seen in this study could be due to changes in sympathetic function. However, further studies are needed to solve this problem.

**Exercise:** This study also demonstrates that lisinopril plus low salt diet or hydrochlorothiazide exerts good BP control during dynamic exercise. However, the BP reduction tended to be somewhat less at the greater workloads than under resting conditions. In both groups the hemodynamic mechanism for BP reduction during exercise was reduction of total peripheral resistance index. In the diuretic group a slight decrease in cardiac index also contributed to the BP reduction. Only minor changes were seen in heart rate, and as in previous studies on other converting enzyme inhibitors, both the heart rate and BP responses to exercise were unchanged after treatment. 15,24 Thus, the sympathetic reflex mechanisms were undisturbed.

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0.1 mg/hr, 0.2 mg/hr, 0.4 mg/hr, 0.6 mg/hr\*

# Helps angina patients get more out of life

Significantly reduces both the frequency of anginal attacks and the need for sublingual nitroglycerin!

Preferred by patients over 7 to 1 for convenience compared to their previous long-acting oral nitrate; only 12% had no preference  $(n = 4,300)^2$ 

All transdermal nitroglycerin products are being marketed pending final evaluation of effectiveness by the FDA. Please consult brief summary of Prescribing Information on the following page.

\*Formerly designated as 2.5 mg/24 hr, 5 mg/24 hr, 10 mg/24 hr, 15 mg/24 hr

Summit Pharmaceuticals
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# Transderm-Nitro®

Transdermal Therapeutic System

# Revised Dosage Information

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

## INDICATIONS AND USAGE

INDICATIONS AND USAGE
This drug product has been conditionally approved by the FDA for the prevention of angina pectoris due to coronary artery disease. Tolerance to the antianginal effects of nitrates (measured by exercise stress testing) has been shown to be a major factor limiting efficacy when transdermal nitrates are used continuously for longer than 12 hours each day. The development of tolerance can be affected (greeneded). development of tolerance can be altered (prevented o

development of tolerance can be altered (prevented or attenuated) by use of a noncontinuous (intermittent) dosing schedule with a nitrate-free interval of 10-12 hours. Controlled clinical trial data suggest that the intermittent use of nitrates is associated with decreased exercise tolerance, in comparison to placebo, during the last part of the nitrate-free interval; the clinical relevance of this observation is unknown, but the possibility of increased frequency or severity of angina during the nitrate-free interval should be considered. Further investigations of the tolerance phenomenon and best regimen are ongoing. A final evaluation of the effectiveness of the product will be announced by the FDA.

Allergic reactions to organic nitrates are extremely rare, but they do occur. Nitroglycerin is contraindicated in patients who are allergic to it. Allergy to the adhesives used in nitroglycerin patches has also been reported, and it similarly constitutes a contraindication to the use of this product.

WARNINGS
The benefits of transdermal nitroglycerin in patients with acute myocardial infarction or congestive heart failure have not been established. It one elects to use nitroglycerin in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia. A cardioverter/defibrillator should not be discharged through a paddle electrode that overlies a Transderm-Nitro patch. The arcing that may be seen in this situation is harmless in itself, but it may be associated with local current concentration that can cause damage to the paddles and burns to the patient.

# PRECAUTIONS

General
Severe hypotension, particularly with upright posture, may occur
with even small doses of nitroglycerin. This drug should therefore
be used with caution in patients who may be volume depleted or
who, for whatever reason, are already hypotensive. Hypotension
induced by nitroglycerin may be accompanied by paradoxical
bradycardia and increased angina pectoris.
Nitrate therapy may aggravate the angina caused by hypertrophic
cardiomynoathy

cardiomyopathy.

As tolerance to other forms of nitroglycerin develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is somewhat blunted.

observable, is somewhat blunted.

In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence.

Several clinical trials in patients with angina pectoris have evaluated nitroglycerin regimens which incorporated a 10-12 hour nitrate-free interval. In some of these trials, an increase in the frequency of anginal attacks during the nitrotacters interval was

ntrate-tree interval. In some of these trials, an increase in the frequency of anginal attacks during the nitrate-free interval was observed in a small number of patients. In one trial, patients demonstrated decreased exercise tolerance at the end of the intrate-free interval. Hemodynamic rebound has been observed only rarely, on the other hand, few studies were so designed that rebound, if it had occurred, would have been detected. The importance of these observations to the routine, clinical use of transfermal nitroglycerin is unknown.

# Information for Patients

Information for Patients
Daily headaches sometimes accompany treatment with nitroglycerin. In patients who get these headaches, the headaches may be a
marker of the activity of the drug. Patients should resist the
temptation to avoid headaches by altering the schedule of their
treatment with nitroglycerin, since loss of headache may be
associated with simultaneous loss of anthanginal efficacy.
Treatment with nitroglycerin may be associated with lightheadedness on standing, especially just after riging from a recumbent or.

ness on standing, especially just after rising from a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol.

# The only patch with an easy-open tab

# Easy to apply — Easy to remove

Available in four convenient strengths

Patches shown are not actual size.

After normal use, there is enough residual nitroglycerin in discarded patches that they are a potential hazard to children and

A patient leaflet is supplied with the systems

A patient leaner is supplied with the systems. **Drug Interactions**The vasodilating effects of nitroglycerin may be additive with those of other vasodilators. Alcohol, in particular, has been found to exhibit additive effects of this variety.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term animal studies have examined the carcinogenic or
mutagenic potential of nitroglycerin. Nitroglycerin's effect upon
reproductive capacity is similarly unknown.

Pregnancy Category C

Animal reproduction studies have not been conducted with nitroglycerin. It is also not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers
It is not known whether nitroglycerin is excreted in human milk.
Because many drugs are excreted in human milk, caution should exercised when nitroglycerin is administered to a nursing woman.

Pediatric Use Safety and effectiveness in children have not been established

## ADVERSE REACTIONS

ADVERSE REACTIONS
Adverse reactions to nitroglycerin are generally dose-related, and almost all of these reactions are the result of nitroglycerin's activity as a vasodilator. Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Transient episodes of lightheadenderses, occasionally related to blood pressure changes, may also occur. Hypotension occurs infrequently, but in some patients if may be severe enough to warrant discontinuation of patients it may be severe enough to warrant discontinuation of

herapy. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.

Extremely rarely ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients. Methemoglobinemia is so infrequent at these doses that further discussion of its diagnosis and treatment is deferred (see Overdosage).

Application-site irritation may occur but is rarely severe. In two placebo-controlled trials of intermittent therapy with nitroglycerin patches at 0.2 to 0.8 mg/hr, the most frequent adverse reactions among 307 subjects were as follows:

	Placebo	Patch
dache	18%	63%
ntheadedness	4%	6%
otension, and/or syncope	0%	4%
eased angina	2%	2%
ntheadedness otension, and/or syncope	4% 0%	

# OVERDOSAGE

OVERDOSAGE
Hemodynamic Effects
The ill effects of nitroglycerin overdose are generally the result of nitroglycerin's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever: vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort, diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures; and death. Laboratory determinations of serum levels of nitroglycerin and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of nitroglycerin overdose.

nave, in any event, no established the in the interest of the

not known which, if any, of these substances can usefully be removed from the body by hemodialysis.

No specific antagonist to the vasodilator effects of nitroglycerin is known, and no intervention has been subject to controlled study as a therapy of nitroglycerin overdose. Because the hypotension associated with nitroglycerin overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward an increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary. The use of epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good. In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of nitroglycerin overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Methemoglobinemia
Nitrate ions liberated during metabolism of nitroglycerin can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b₅ reductase activity, however, and even assuming that the nitrate moleties of nitroglycerin are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of nitroglycerin should be required before any of these patients manifests clinically significant (≥ 10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of nitroglycerin. In one study in which 36 patients received 2-4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr, the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations, there are case reports of

Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible.

Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO<sub>2</sub>. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1-2 mg/kg intravenously.

## DOSAGE AND ADMINISTRATION

DUSAGE AND JUMINISTRATION
The suggested starting dose is between 0.2 mg/hr\*, and
0.4 mg/hr\*. Doses between 0.4 mg/hr\* and 0.8 mg/hr\* have
shown continued effectiveness for 10-12 hours daily for at least
one month (the longest period studied) of intermittent administration. Although the minimum nitrate-free interval has not been defined, data show that a nitrate-free interval of 10-12 hours is sufficient (see CLINICAL PHARMACOLOGY). Thus, an appropriate dosing schedule for nitroglycerin patches would include a daily patch-on period of 12-14 hours and a daily patch-off period of 10-12 hours.

10-12 hours.
Although some well-controlled clinical trials using exercise tolerance testing have shown maintenance of effectiveness when patches are worn continuously, the large majority of such controlled trials have shown the development of tolerance (i.e., complete loss of effect) within the first 24 hours after therapy was initiated. Dose adjustment, even to levels much higher than generally used, did not restore efficacy.

PATIENT INSTRUCTIONS FOR APPLICATION OF SYSTEM

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Transderm- Nitro System*	Nitro- glycerin in System	System Size	Carto	on			
0.1 mg/hr	12.5 mg	- 10 10 10	**30	Systems. Systems.	NDC	57267	-902-4
0.2 mg/hr	25 mg	10 cm <sup>2</sup>	100	Systems. Systems.	NDC	57267 57267	-902-31 -905-20
0.4	50		100	Systems. Systems.	NDC	57267	-905-30
0.4 mg/hr	50 mg	THE REAL PROPERTY.	**30	Systems. Systems.	NDC	57267	-910-42
0.6 mg/hr	75 mg	30 cm <sup>2</sup>	30	Systems. Systems. Systems.	NDC	57267	-915-26
				Systems.			

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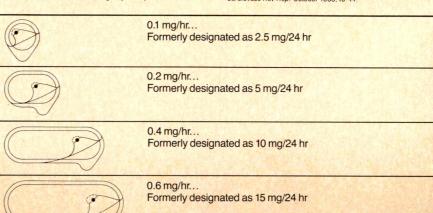
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# Effect of Postural Stimulation on Systemic Hemodynamics and Sympathetic Nervous Activity in Systemic Hypertension

Joseph L. Izzo, Jr., MD, Emilee Sander, BS, and Patricia S. Larrabee, RN, MS

The contributions of the carotid sinus and cardiopulmonary baroreflexes to the interindividual variation in sympathetic nervous system activation caused by postural adaptation were indirectly assessed in 68 mild hypertensive subjects. Supine and upright plasma norepinephrine (NE), blood pressure (cuff) and cardiac output (acetylene rebreathing) were measured. Mean arterial pressure (MAP), carotid sinus pressure, stroke volume and systemic vascular resistance were calculated. Stroke volume was assumed to be proportional to the degree of stretch of cardiac mechanoreceptors, carotid sinus MAP was assumed to be proportional to carotid sinus stretch and plasma NE to reflect sympathetic nervous activity. Plasma NE correlated inversely with stroke volume (r = -0.62, p <10<sup>-14</sup>) and estimated carotid sinus MAP (r = -0.33, p <0.0002) and positively with systemic vascular resistance (r = 0.59, p  $< 10^{-10}$ ). Holding systemic vascular resistance constant by partial regression, the inverse relation between plasma NE and stroke volume remained (partial r = -0.36, p <0.02). Multiple linear regression yielded the equation: plasma NE (pg/ml) = 720 + 4.3 age - 5.1 stroke volume(ml) - 1.0 carotid sinus MAP (mm Hg). Substituting mean supine and upright values for stroke volume and carotid sinus MAP in this equation, it can be roughly estimated that changes in stroke volume account for as much as 60% of the postural variation in plasma NE in hypertensives, whereas only 15% of this variation is caused by changes in carotid sinus pressure. These findings suggest that cardiopulmonary baroreflexes are primary activators of the sympathetic nervous system during postural adaptation. Because plasma NE tends to be elevated in hypertension, cardiopulmonary baroreflexes may also be abnormal in this condition.

Instantaneous hemodynamic adaptation to upright posture is made possible by the simultaneous stimulation of sympathetic function that occurs when decreased carotid sinus hydrostatic pressure and decreased cardiac arterial pressure act in concert to "unload" both sets of mechanoreceptors. The resultant sympathetic discharge during upright posture and the subsequent peripheral vasoconstriction and increased heart rate help maintain flow to the central nervous system during upright posture.

The present study was undertaken to assess indirect-

The present study was undertaken to assess indirectly whether the sympathetic nervous response to postural adaptation is dependent more on the cardiopulmonary or the carotid sinus baroreflex. We studied a cross-section of healthy patients with mild essential hypertension after equilibration in both the supine and upright positions. We equated changes in plasma norepinephrine (NE) with changes in sympathetic-dependent vasomotor tone. We also assumed proportionality of cardiac stroke volume and central stretch and cardiopulmonary baroreflex input. Changes in estimated arterial baroreflex input were approximated by estimating postural changes in carotid sinus pressure.

# METHODS

Subject selection and qualification: An interview and physical examination were conducted in 75 male subjects, age 21 to 67 years, with hypertension previously documented on at least 3 occasions. Subjects who demonstrated no signs or symptoms compatible with secondary forms of hypertension were subsequently withdrawn from all medications. Patients with diabetes, obstructive lung disease, obesity, symptomatic coronary artery disease or other conditions that precluded withdrawal of antihypertensive therapy were excluded. Prior antihypertensive drug therapy was withdrawn in 70 patients who received placebo for 1 month, while 5 others had never received therapy. Patients monitored blood pressures at home and returned weekly for follow-up visits. Any subject whose blood pressure was >200 mm Hg systolic or >115 mm Hg diastolic during the placebo phase was excluded from further study and returned to the previous regimen. Sixty-eight men qualified as having "mild to moderate" hypertension at the fourth week of study, when the mean of 3 recordings of sitting diastolic blood pressure was required to be in the range of 90 to 110 mm Hg.

Study day protocol: After blood pressure qualification in the outpatient clinic, subjects were sent to the clinical laboratory, where a needle was inserted into a forearm vein and a heparin lock attached. After sub-

From the Department of Medicine, State University of New York at Buffalo, Buffalo, New York, and School of Medicine and Dentistry, University of Rochester, Rochester. This study was supported in part by grants from the Genesee Valley Chapter of New York State Affiliate of the American Heart Association, the Squibb Institute for Medical Research, Princeton, New Jersey, and the Eli Lilly Medical Research Institute, Indianapolis, Indiana. Manuscript received May 22, 1989; revised manuscript received September 29, 1989, and accepted September 30.

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TABLE I Group Characterist	ics		
Variables	Supine	Upright	p Value*
Blood pressure (mm Hg)	142 ± 2/	140 ± 2/	NS
	93 ± 1	$99 \pm 1$	<10-7
Carotid sinus MAP (mm Hg)	109 ± 2	77 ± 1	<10-40
Heart rate (beats/min)	74 ± 1	85 ± 2	<10-20
Cardiac output (liters/min)	$6.7 \pm 0.2$	$5.1 \pm 0.1$	<10-18
Stroke volume (ml)	92 ± 2	61 ± 2	<10-26
Systemic vascular resistance (dynes · s · cm <sup>-5</sup> )	1,370 ± 45	$1,850 \pm 50$	<10-20
Plasma norepinephrine (pg/ml)	$321 \pm 14$	$568 \pm 25$	<10-21
Plasma epinephrine (pg/ml)	32 ± 2	45 ± 3	<10-7

	Stroke Volume	Systemic Vascular Resistance	MAP	Carotid Sinus MAP	Age (yrs)
Plasma norepinephrine	-0.62 <sup>‡</sup>	0.59‡	0.31*	-0.33*	0.25*
Age	-0.08	0.40 <sup>†</sup>	0.33*	0.21*	
Carotid sinus MAP	0.52 <sup>†</sup>	0.07	0.47†		
MAP	-0.14	0.50 <sup>†</sup>			
Systemic vascular resistance	-0.71§				

These correlation coefficients are based on 136 data points (69 supine and 68 upright). \* p <0.02, † p <10<sup>-6</sup>, † p <10<sup>-10</sup>,  $\S$  p <10<sup>-14</sup>. MAP = mean arterial pressure.

ì			
	TABLE III Multiple Lin	near and Partia	al Regressions
	Forced equation:		
	Plasma NE (pg/ml) = 7	20 + 4.3 age (yi	rs) - 5.1 SV (ml) - 1.0 MAP
	(mm Hg) (carotid sin	us)	
1	Multiple $R = 0.66$ (p <1	$0^{-16}$ )	
ì	Component analysis of fo	rced equation:	
	Variable	F-to-remove	P Value
	SV	54.5	10 <sup>-10</sup>
i	Age (yrs)	11	0.002
į	MAP (carotid sinus)	1.35	0.25
	Partial regression:		
į	Plasma NE is proportion	nal to SV at cons	tant SVR (partial $r = -0.36$ ,
1	p < 0.0002)		

MAP = mean arterial pressure; NE = norepinephrine; SV = stroke volume; SVR = systemic vascular resistance.

jects remained undisturbed for at least 15 minutes, a blood sample for plasma catecholamines was withdrawn, immediately iced and stored with EDTA and reduced glutathione before analysis. Subjects then had 4 blood pressures determined in the supine position by a single observer using standard cuff technique, 1 before and 1 after each duplicate measurement of cardiac output (CO) and heart rate. CO was determined by a previously described acetylene-helium rebreathing technique. 1,2 The mean of the 4 blood pressure values was subsequently used to calculate mean arterial pressure (MAP, diastolic + 1/3 pulse pressure) and systemic vascular resistance (MAP/CO  $\times$  80, dynes  $\cdot$  s  $\cdot$  cm<sup>-5</sup>).

After completion of the supine phase (approximately 25 to 30 minutes), subjects stood quietly and were restudied in identical fashion to that described for the su-

pine position. Plasma catecholamine sampling occurred about 10 minutes after assumption of the upright pos-

Plasma catecholamines were measured by a modified radioenzymatic technique that has been previously characterized and validated in our laboratory.<sup>3,4</sup> In 35 subjects, plasma catecholamines were determined both before and after supine hemodynamic testing; the means of the values obtained after hemodynamic testing were identical to those obtained before hemodynamic testing, indicating that the rebreathing test had no appreciable effect on sympathoadrenal activity.

To estimate the change in carotid sinus pressure caused by hydrostatic pressure decreases in the upright position, we used the consistent anatomic relation between the angle of the jaw (representing the anatomic location of the carotid sinus) and the brachial artery (representing the pressure obtained by cuff determination). As a result of measurements in 25 subjects, we found that the carotid-brachial distance is consistently 26% of height (r = 0.83). Transforming this relation to orthostatic blood pressure changes, carotid sinus pressure in the upright position (mm Hg) can be estimated as brachial arterial pressure minus 0.20 height (cm). In the supine position, pressures at the brachial artery and carotid sinus were assumed to be equal.

Basic statistical techniques were used, including paired Student t tests to compare supine to upright variables. Pearson linear regressions were used to relate plasma NE to stroke volume or estimated carotid sinus pressure. However, to use indirect changes in stroke volume to infer the sympathoadrenal impact of altered atrial stretch, it was necessary to account for the potential confounding relation that exists between decreased upright stroke volume and increased upright systemic vascular resistance. Because stroke volume is related negatively to arterial impedance (and resistance), any potential interpretation of the negative correlation between plasma NE and stroke volume could be affected by arterial hemodynamic events. To help solve this problem, the technique of partial regression was used to hold systemic vascular resistance (the confounding term) constant mathematically while studying the direct relation between stroke volume and plasma NE. Forced multiple linear regression was used to identify the relative ranking of components contributing to plasma NE values.5

# RESULTS

The 68 subjects averaged 48 ± 1 years of age and weighed  $84 \pm 2$  kg (mean  $\pm 1$  standard error). The effect of postural change on the study variables is listed in Table I. The exceptionally high degree of statistical significance in many of these terms indicates the consistency of postural change as a hemodynamic stimulus. Figure 1 shows the strong negative correlation between respective supine and upright values of stroke volume and plasma NE (r = -0.62,  $p < 10^{-14}$ , n = 136). Not shown in Figure 1 are the separate correlations obtained for supine (r = -0.43, p < 0.001, n = 68) or upright (r = -0.43, p < 0.001, n = 68)= -0.40, p < 0.0001, n = 68) stroke volume against corresponding supine or upright plasma NE values. Supine MAP correlated positively with supine plasma NE (r = 0.50, p < 0.0002, n = 68) but there was no relation between upright carotid sinus MAP and upright plasma NF

Figure 2 shows the weaker negative correlation between estimated carotid sinus MAP and plasma NE. Table II lists the correlation matrix of study variables. Table III lists multiple and partial regression data. The relation between stroke volume and plasma NE is not solely determined by arterial hemodynamic changes, because even when systemic vascular resistance is held constant by partial regression, a significant negative correlation between stroke volume and plasma NE remains. Regression coefficients from multiple linear regression demonstrate the greater weighing of stroke volume (-5.1) compared to carotid sinus pressure (-1.0) in determining plasma NE.

# DISCUSSION

Despite the complex nature of the determinants of stroke volume, present data suggest a primary role for the cardiopulmonary baroreflex system in postural adaptation. During postural adaptation, stroke volume and carotid sinus pressure are decreased consistently by about 33%. Because of the higher gain of the cardiopulmonary system on sympathetic activity, this "low pressure" system would be expected to exert a greater influence than the arterial stretch receptor during periods of decreased flow or pressure.

Present correlative data, although indirect, also can be used in more complicated theoretical calculations. The simple correlation coefficients between stroke volume and plasma NE (r = -0.62) and between estimated carotid sinus pressure and plasma NE (r = -0.33) differ widely in their physiologic impact, which relates more closely to the squares of these numbers. By these estimations, stroke volume is 3 to 4 times more powerful than estimated carotid sinus pressure in determining the postural variation of plasma NE.

The conclusion that the inverse relation between stroke volume and plasma NE is evidence of counterregulation of sympathetic nervous activity by central

FIGURE 1. Correlation between supine and upright plasma norepinephrine (NE) and corresponding values of stroke volume. The high correlation coefficient (r=-0.62) has extraordinary statistical significance ( $p<10^{-14}$ ). This relation represents the input of the cardiopulmonary baroreflexes on the sympathetic nervous system. When supine values alone are used (n=68), the negative correlation persists (n=-0.43), n=0.001), as it does for the corresponding upright values of plasma NE and stroke volume (n=68), n=-0.40, n=0.001).

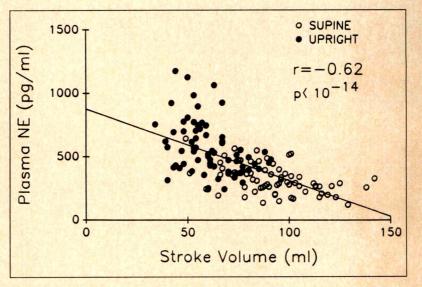
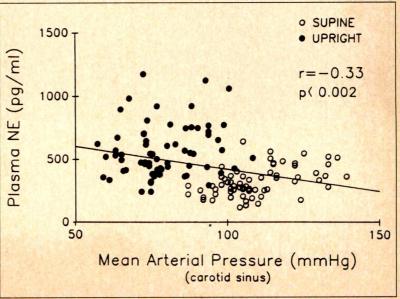


FIGURE 2. Correlation between estimated carotid sinus pressure (see text) and plasma norepinephrine (NE). This weaker relation reflects the lesser input of the carotid sinus on postural sympathetic nervous activation (Figure 1).



blood volume may at first seem to be difficult to substantiate. No other explanation is more convincing, however. Age does not appear to be a confounder of this correlation. However, a potential confounding problem exists in interpretation of present data as a reflection of cardiopulmonary or "venous" events. Increased upright systemic vascular resistance and impedance independently depress stroke volume, perhaps explaining part of the strong reciprocal relation between stroke volume and plasma NE. To help clarify this problem, partial regression was used. This 3-variable analytical technique allows 1 variable to be held constant mathematically while the relation between the other 2 is investigated. In this way, the potential influence of a "confounding" variable can be assessed. In the present study, when systemic vascular resistance was held constant, the negative relation between stroke volume and plasma NE persisted. When stroke volume was held constant by the same technique, no residual relation between carotid sinus pressure and plasma NE remained.

Multiple linear regression also helped establish the relative contributions of both baroreflexes to sympathetic activation. The regression coefficient for stroke volume on plasma NE is -5.1, while the corresponding coefficient for estimated mean carotid sinus pressure is -1.0. Because orthostatic changes in stroke volume decrease to 61 ml from 92 ml (upright vs supine), the contribution of postural stroke volume change to the corresponding postural change in plasma NE is about 150 pg/ml (5.1  $\times$  92 - 5.1  $\times$  61). Because the observed average postural increase in plasma NE is about 250 pg/ml, it can be argued indirectly that cardiopulmonary baroreflexes account for about 60% of the postural increase in sympathetic nervous activity. In contrast, using similar arithmetic, carotid sinus pressure changes account for about 15% of the observed postural differences in plasma NE. It is clear that such simplistic calculations cannot be directly related to physiologic events. Nevertheless, the cardiopulmonary baroreflex may be as much as 4 times more important than the carotid sinus in the sympathoadrenal activation of normal postural adaptation. This ratio fits reasonably well with the 3:1 ratio of relative importance of the 2 stimulatory variables estimated by the squares of the correlation coefficients of the plasma NE versus stroke volume and plasma NE versus carotid sinus MAP equations.

In dogs and man, ample corroboration of the physiologic role of cardiopulmonary baroreflexes in the control of sympathoadrenal activity already exists. Ample data strongly suggest that cardiac atrial distention suppresses systemic and renal vasoconstriction.<sup>6-14</sup> The supposition that the cardiopulmonary system is important in postural adaptation appears to have clinicopathologic correlations as well. For example, orthotopic cardiac transplantation impairs the cardiopulmonary baroreflex.<sup>14</sup> Ab-

normal cardiopulmonary baroreflexes may explain in part why transplant recipients have orthostatic hypotension despite having intact carotid sinus function. Another group of patients with orthostatic hypotension may have abnormal cardiopulmonary baroreflexes. We have found 3 individuals with normal supine plasma NE and subnormal postural increases in plasma NE. According to the criteria of Ziegler et al<sup>15</sup> these patients have primary orthostatic hypotension. Bradycardic responses to Valsalva or phenylephrine were normal in these patients, however, and 1 of them was able to increase blood pressure in response to cold pressor stimulation (Izzo, unpublished observations). Thus, it can be argued that the autonomic dysfunction in these patients is not associated with abnormalities of carotid sinus baroreflexes or efferent sympathetic fibers, and may be related more directly to abnormal cardiopulmonary baroreflexes. Potential abnormalities of cardiopulmonary baroreflexes in essential hypertension are also conceivable, but would be opposite to the pattern observed in patients with orthostatic hypotension.

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1.0%

Data from the ASSET study (N = 5,013) reported the overall risk of post-MI stroke with Activase\* (1.1%) was comparable to placebo (1.0%).2

Bleeding is the most common complication of thrombolytic therapy, with intracranial bleeding being the most serious. Activase® is contraindicated in patients with: active internal bleeding, history of cerebrovascular accident, recent (within two months) intracranial or intraspinal surgery or trauma, intracranial neoplasm, arteriovenous malformation, or aneurysm, known bleeding diathesis, severe uncontrolled hypertension. (See WARNINGS section of brief summary of prescribing information.)

# OPTIMIZE THERAPEUTIC BENEFITS THROUGH PROPER PATIENT SELECTION

# Therapeutic window within 6 hours of onset of symptoms

The benefits of thrombolytic activity are demonstrated up to 6 hours after the onset of symptoms

# Therapeutic benefits in patients up to 75 years of age

Proven reduction in mortality in patients up to 75 years of age when used within 5 hours of acute MI onset<sup>2</sup>

# Easy-to-follow dosing guidelines



Standard dose: 100 mg

For patients less than 65 kg: 1.25 mg/kg

Initiate lytic dose as follows: 60% of total therapeutic dose should be administered in the first hour of which 6-10 mg should be administered as bolus. The remaining 40% is delivered over the next 2 hours



# References

 TIMI Study Group: Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction: Results of the Thrombolysis in Myocardial Infarction (TIMI) Phase II Trial. N Engl J Med 1989;320(10):618-627.

2. Wilcox RG, Olsson CG, Skene AM et al: Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction. *Lancet* 1988;2:525-530.

Genentech, Inc.

Please see brief summary of prescribing information on facing page. © 1989 Genentech\* Inc.



Brief Summary Consult full prescribing information before using.

INDICATIONS AND USAGE: ACTIVASE\* is indicated for use in the management of acute myocardial infarction (AMI) in adults for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI. Treatment should be initiated as

tive heart failure and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms.

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, ACTIVASE® is contraindicated in the following situations: Active internal bleeding • History of cerebrowing lar accident • Recent (within two months) intracranial or intraspinal surgery or trauma (see WARNINGS) • Intracranial neoplasm, arteriovenous malformation, or aneurysm • Known bleeding

warnings) - intracranial neuplasini, arteriovenous minorimation, of alleutysin - known bleeding diathesis - Severe uncontrolled hypertension.

WARNINGS: Bleeding The most common complication encountered during ACTIVASE® therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g.,

sites of venous cutdown, arterial puncture, recent surgical intervention).

Concomitant use of heparin anticoagulation may contribute to bleeding. Some hemorrhagic episodes occurred one or more days after the effects of ACTIVASE® had dissipated, but while heparin therapy

Concomitant use of heparin anticoagulation may contribute to bleeding. Some hemorrhagic episodes occurred one or more days after the effects of ACTIVASE® had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during ACTIVASE® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including sites of catheter insertion, arterial and venous puncture, cutdown and needle puncture). Intramuscular injections and nonessential handling of the patient should be avoided during treatment with ACTIVASE® view injections and nonessential handling of the patient should be avoided during treatment with ACTIVASE® view injections and nonessential handling of the patient should be avoided or at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding. Should serious bleeding (not controllable by local pressure) occur, the infusion of ACTIVASE® and any concomitant heparin should be terminated immediately. Each patient being considered for therapy with ACTIVASE® should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

In the following conditions, the risks of ACTIVASE® therapy may be increased and should be weighed against the anticipated benefits. Recent (within 10 days) major surgery, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels · Cerebrovascular disease · Recent (within 10 days) gastrointestinal or genitourinary bleeding · Recent (within 10 days) trauma · Hypertension: systolic BP≥100 mm Hg and/or diastolic BP≥110 mm Hg · High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation · Acute pericarditis · Subacute bacterial endocarditis · Hemostatic defects including those secondary to severe hepatic or renal disease · Significant liver dysfunction · Pregnancy · Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions · Septic

extent mitigate this phenomenon.

Drug Interactions The interaction of ACTIVASE® with other cardioactive drugs has not been studied addition to blending acceptable with benefit and the property of the prope

Drug Interactions The interaction of ACTIVASE® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function may increase the risk of bleeding if administered prior to, during or after ACTIVASE® therapy. Use of Anticoagulants Heparin has been administered concomitantly with and following infusions of ACTIVASE® to reduce the risk of rethrombosis. Because either heparin or ACTIVASE® alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites. Pregnancy (Category C) Animal reproduction studies have not been conducted with ACTIVASE® It is also not known whether ACTIVASE® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ACTIVASE® should be given to a pregnant woman only if clearly needed

Pediatric Use Safety and effectiveness of ACTIVASE® in children has not been established

remartic use Salety and effectiveness of ACTIVASE® in children has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which evaluated tumorigenicity of ACTIVASE® and effect on tumor metastases in rodents, were negative. Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure and only at the highest concentrations tested.

Nursing Mothers It is not known whether ACTIVASE® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ACTIVASE® is administered to a

nursing woman.

ADVERSE REACTIONS: Bleeding The most frequent adverse reaction associated with ACTIVASE® is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

The following incidence of significant internal bleeding (estimated as > 250 cc blood loss) has been reported in studies in over 800 patients treated at all doses:

The incidence of intracranial bleeding in patients treated with ACTIVASE®, Alteplase, recombinant, is as follows:

		The last of the la
Dose	Number of Patients	<u>%</u>
100 mg	3272	0.4
150 mg	1779	1.3
1-1.4 mg/kg	237	0.4

These data indicate that a dose of 150 mg of ACTIVASE® should not be used because it has been associated with an increase in intracranial bleeding.

Recent data indicate that the incidence of stroke in 6 randomized double-blind placebo controlled trials¹¹ is not significantly different in the ACTIVASE® treated patients compared to those treated with placebo (37/3161, 1.2% versus 27/3092, 0.9%, respectively) (p = 0.26).

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial), occur, ACTIVASE® therapy should be discontinued immediately, along with any concomitant.

ACTIVASE® therapy should be discontinued immediately, along with any concomitant

dial) occur. ACTIVASE® therapy should be discontinued immediately, along with any concomitant therapy with heparin.

Fibrin, which is part of the hemostatic plug formed at needle puncture sites, will be lysed during ACTIVASE® therapy. Therefore, ACTIVASE® therapy requires careful attention to potential bleeding sites. Allergic Reactions No serious or life-threatening allergic reactions have been reported. Other mild hypersensitivity reactions such as urticaria have been observed occasionally.

Other Adverse Reactions Other adverse reactions have been reported, principally nause and/or vomitting, hypotension, and fever. These reactions are frequent sequelae of MI and may or may not be attributable to ACTIVASE® therapy.

DOSAGE AND ADMINISTRATION: Administer ACTIVASE® as soon as possible after the onset

of symptoms.

ACTIVASE® is for intravenous administration only.

The recommended dose is 100 mg administration only.

The recommended dose is 100 mg administered as 60 mg (34.8 million IU) in the first hour (of which 6 to 10 mg is administered as a bolus over the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 mg (11.6 million IU) over the third hour. For smaller patients (less than 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.8

A DOSE OF 150 MG OF ACTIVASE\* SHOULD NOT BE USED BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Although the use of anticoagulants and antiplatelet drugs during and following administration of ACTIVASE\* has not been shown to be of unequivocal benefit, heparin has been administered concomitantly for 24 hours or longer in more than 90% of patients. Aspirin and/or dipyridamole have been given either during and/or following heparin treatment.

Reconstitution and Dilution DO NOT USE IF VACUUM IS NOT PRESENT.

ACTIVASE\* should be reconstituted by asentically adding the appropriate volume of the accompany.

ACTIVASE\* should be reconstituted by aseptically adding the appropriate volume of the accompaing Sterile Water for Injection, USP to the vial. It is important that ACTIVASE\* be reconstituted only we Sterile Water for Injection, USP without preservatives. Do not use Bacteriostatic Water for Injection USP The reconstituted preparation results in a colorless to pale yellow transparent solution containing ACTIVASE\* 1.0 mg/mL at approximately pH 7.3. The osmolality of this solution is approximately

215 mOsm/kg.

Because ACTIVASE® contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution may be used for intravenous administration within 8 hours following reconstitution when stored between 2-30°C. Before further dilution or administration, the product should be lly inspected for particulate matter and discoloration prior to administration whenever solution and

container permit.

ACTIVASE® is stable for up to 8 hours in these solutions at room temperature. Exposure to light has no effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, e.g., Sterile Water for Injection, USP or preservative-containing solutions for further dilutions.

mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other influsion solutions, e.g., Sterile Water for Injection, USP or preservative-containing solutions for further dilution. No other medication should be added to influsion solutions containing ACTIVASE\*. Any unused influsion solution inshould be discarded. HOW SUPPLIED: ACTIVASE\* is supplied as a sterile, lyophilized powder in 20 mg and 50 mg vials containing vacuum, each packaged with diluent for reconstitution. Storage Store lyophilized ACTIVASE\* at controlled room temperature not to exceed 30°C (86°F), or under refrigeration (2-8°C/36-46°F). Protect the lyophilized material during extended storage from excessive exposure to light.

Do not use beyond the expiration date stamped on the vial.

ACTIVASE\* Alteplase, recombinant Manufactured by

Manufactured by GENENTECH® INC. 460 Point San Bruno Blvd. South San Francisco, CA 94080

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1. Topol, E. J., Morriss, D.C., Smalling, R.W., et al., A Multicenter, Randomized, Placebo-Controlled Trial of a New Form of Intravenous Recombinant Tissue-Type Plasminogen Activator (Activase\*) in Acute Myocardial Infarction. J Am. Coll. Card. 9:1205-1213, 1987. 2. Guerci, A.D., Gerstenblith, G., Brinker, J.A., et al., A Randomized Trial of Intravenous Tissue Plasminogen Activator for Acute Myocardial Infarction with Subsequent Randomization of Elective Coronary Angioplasty. New Engl. J. Med., 317:1613-618, 1987. 3. O'Rourke, M., Baron, D., Keogh, A., et al., Limitation of Myocardial Infarction by Early Infusion of Recombinant Tissue-Plasminogen Activator, Circulation, 77:1311-1315, 1988. 4. Wilcox, R.G., von der Lippe, G., Olsson, C.G., et al., Trial of Tissue Plasminogen Activator for Mortality Reduction in Acute Myocardial Infarction: ASSET. Lancet 2:525-530, 1988. 5. Hampton, J.R., The University of Nottingham, Personal Communication. 6. Van de Werf, F., Arnold A.E.R., et al., Effect of Intravenous Tissue-Plasminogen Activator on Infarct Size, Left Ventricular Function and Survival in Patients with Acute Myocardial Infarction. Br. Med. J., 297:1374-1379, 1988. 7. National Heart Foundation of Australia Coronary Thrombolysis Group: Coronary Thrombolysis Gr

	Total Dose ≤ 100 mg	Total Dose > 100 mg
gastrointestinal	5%	5%
genitourinary	4%	4%
ecchymosis	1%	<1%
retroperitoneal	<1%	<1%
	<1%	<1%
epistaxis gingiyal	<1%	<1%

# Genentech: Inc.



# THE ROLE OF INSULIN RESISTANCE: A NEW DIMENSION IN HYPERTENSION

Saturday, March 17, 1990

The New Orleans Hilton Riverside & Towers New Orleans, Louisiana

4:30 pm-5:45 pm

Registration—Chemin Royale

and

Buffet—Grand Salon C

6:00 pm-9:30 pm 9:30 pm-10:30 pm Symposium—Grand Ballroom C & D

Reception With Faculty—Grand Salon C

# CHAIRMAN

Norman M. Kaplan, MD

Professor of Internal Medicine Chief, Hypertension Division University of Texas Southwestern Medical Center at Dallas Dallas, Texas

Is the Failure to Prevent CAD by Treating Hypertension Related to Insulin Resistance?

Norman K. Hollenberg, MD, PhD

Discussion

What is the Clinical Impact of Insulin Resistance as a Risk Factor?

Ralph A. DeFronzo, MD

Discussion

Does Hypertension Contribute to the Atherosclerotic Process and Can it be Prevented?

Aram V. Chobanian, MD

Discussion

Antihypertensive Agents and Risk Factors: Does Choice of Therapy Make a Difference?

Henry R. Black, MD

Discussion

Hypertension Management: How Can We Maximally Reduce Cardiovascular Risk?

Norman M. Kaplan, MD

Discussion

As an organization accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians, the Postgraduate Medical Institute, Waltham, Massachusetts, designates this continuing medical education activity for 3 credit hours in Category 1 of the Physician's Recognition Award of the American Medical Association.

# Usefulness of Nicorandil in Congestive Heart Failure

Nazzareno Galié, MD, Elisabetta Varani, MD, Luigi Maiello, MD, Giuseppe Boriani, MD, Stefano Boschi, ScD, Giorgio Binetti, MD, and Bruno Magnani, MD

Rest and exercise hemodynamic and hormonal effects of nicorandil, a nicotinamide-nitrate vasodilator, were assessed in 9 patients with New York Heart Association class II or III congestive heart failure (CHF) and left ventricular ejection fraction ≤40%. Single oral doses of placebo and 40 and 60 mg of nicorandil were given in a double-blind, randomized trial. Hemodynamic measurements were assessed at rest, up to 8 hours after dose and at peak exercise performed on an upright cycloergometer 1 hour after the dose. Forearm blood flow and venous capacitance were measured by plethysmography 45 minutes after dose. Plasma noradrenaline and plasma renin activity were assessed 1 hour and 2 hours after dose, respectively. Data were analyzed by analysis of variance. Peak effects were observed between 30 and 60 minutes after dose. Mean blood pressure decreased from 86  $\pm$  7 mm Hg after placebo to 78  $\pm$  7 mm Hg after 40 mg (p <0.05) and to 78  $\pm$  7 mm Hg after 60 mg (p <0.05) of nicorandil. Mean pulmonary artery pressure decreased from 24  $\pm$  11 to 15  $\pm$  17 mm Hg (p <0.05) and to 17  $\pm$  7 mm Hg (p <0.05) and mean pulmonary wedge pressure decreased from 15  $\pm$  8 to 9  $\pm$  4 mm Hg (p <0.05) and to 10  $\pm$  5 mm Hg (p <0.05). The changes were significant up to 6 to 8 hours after both doses. Cardiac output increased 2 hours after dose from 4.6  $\pm$  0.7 liters/ min after placebo to 5.5  $\pm$  0.8 liters/min after 60 mg (p <0.05). At peak exercise mean pulmonary wedge pressure decreased from 29 ± 8 mm Hg after placebo to 24  $\pm$  7 mm Hg (p <0.05) and to 27  $\pm$  8 mm Hg (difference not significant) after 40 and 60 mg of nicorandil. Venous capacitance increased from 2.9  $\pm$  1.4 ml after placebo to 3.4  $\pm$  1.3 ml after 40 mg of nicorandil (p = 0.1). Cardiac output 1 hour after the meal was 5.7  $\pm$  1 liters/min after placebo and increased to 6.3  $\pm$  1.5 liters/min (p <0.05) after 40 mg and to 6.2  $\pm$  1 liters/min (p <0.05) after 60 mg of nicorandil. Plasma renin activity increased from 18.6  $\pm$  29.3 ng/ml/hour after placebo to 24.3  $\pm$  31.1 (p < 0.05) and 22  $\pm$  31.1 ng/ml/hour (p <0.05) after 40 and 60 mg of nicorandil. Single oral doses of nicorandil in patients with CHF induce favorable changes on rest and exercise hemodynamics up to 6 to 8 hours. An increase of renin activity is also observed.

(Am J Cardiol 1990;65:343-348)

icorandil (N-[2-hydroxyethyl]nicotinamide nitrate) is a new vasodilator drug that is structurally a nitrate and also a nicotinamide.1 The mechanism of the relaxant action of nicorandil appears to involve an increase in membrane potassium conductance with membrane hyperpolarization that induces a reduction of calcium influx through voltage-dependent calcium channels and eventually vascular smooth muscle cells relax.2 Moreover, nicorandil, like classic nitrates, increases intracellular cyclic guanosine monophosphate,<sup>3</sup> which is involved in vascular relaxant mechanisms.<sup>4</sup> Previous experimental and clinical data have demonstrated that nicorandil reduces cardiac afterload and preload, showing balanced vasodilation.5-9 In patients with congestive heart failure (CHF), vasodilator therapy improves clinical status, exercise tolerance and survival<sup>10,11</sup> and new drugs with load-reducing activity need to be tested in this condition to find molecules with better pharmacokinetics and lesser side effects and contraindications. Preliminary evaluation of a new drug requires the assessment of the magnitude, dose-response characteristics and time course of hemodynamic effects of single doses. In this study, we compared the effects of 2 single oral doses of nicorandil and placebo on resting and exercise hemodynamics, peripheral circulation and hormonal profile in patients with CHF.

# **METHODS**

Patient selection: Nine patients with New York Heart Association class II or III CHF were entered into the study. Clinical symptoms and signs of chronic (at least 6 months) CHF as well as left ventricular ejection fraction ≤40% were required for inclusion in the study. CHF was due to coronary artery disease diagnosed by a history of previous documented myocardial infarction or coronary arteriography, or was due to idiopathic dilated cardiomyopathy that was diagnosed if no other cause of CHF was apparent. Patients with primary pulmonary or valvular heart disease were excluded. All patients were receiving previous digitalis and diuretic therapy. Vasodilator drugs were withheld at least 15 days before study. Oral witnessed informed consent was obtained from each patient, and the study protocol was approved by the local human studies committee.

From the Istituto di Malattie dell'Apparato Cardiovascolare, Università di Bologna, Italy, and the Servizio di Farmacologia Clinica e Terapia, Università di Bologna, Italy. Nicorandil tablets were supplied by Bracco Spa Laboratories, Milan, Italy. Manuscript received July 24, 1989; revised manuscript received September 25, 1989, and accepted September 26.

Address for reprints: Nazzareno Galiè, MD, Istituto di Cardiologia Policlinico S. Orsola, Via Massarenti 9, 40138 Bologna, Italy.

**TABLE I** Clinical Characteristics Age Cardio-Pt (vrs) NYHA FF thoracio Medications No Sex Diagnosis Class (%) Ratio (mg/day) 28. F IDC 40 0.56 D(0.25), H(50), A(5) 2 44, M IDC III 34 0.57 D(0.25), B(2), C(100) 3 44. M CAD III 23 0.60 D(0.375), B(2) 4 52. F IDC 111 29 0.57 D(0.25), F(50) 5 53. F IDC III 40 0.60 D(0.25), F(50) 6 61. M IDC 111 29 0.63 D(0.25), B(0.5), C(100) 61 F IDC 11 38 0.63 D(0.375), F(25), S(50) 8 63, F IDC 11 20 0.63 D(0.25), H(50), A(5) 9 64, M IDC III 18 0.64 D(0.125), B(1), F(50), C(100) A = amiloride; B = burnetanide; C = canrenone; CAD = coronary artery disease; D = digitalis; EF = ejection fraction; F = furosemide; H = hydrochlorothiazide; IDC = idiopathic dilated cardiomyopathy; NYHA = New York Heart Association; S = spironolactone.

**Procedures:** The day before the beginning of the study a Swan-Ganz thermodilution catheter was positioned in the pulmonary artery to assess pulmonary artery and right atrial pressures. Pulmonary capillary wedge pressure was taken as occluded pulmonary arterial pressure or pulmonary arterial diastolic pressure. Heart rate was monitored by electrocardiogram.

Systemic blood pressure was measured by the standard cuff technique and cardiac output was measured by thermodilution in triplicate (variation of ≤10%). Derived hemodynamic values were calculated by standard formulas. Forearm blood flow was assessed by strain gauge plethysmography and expressed in ml/min/100 g of tissue. 12 Forearm venous capacitance was assessed by strain gauge occlusion plethysmography and expressed in ml for 2 levels of occlusion pressures (30 and 40 mm Hg). 13,14 Upright bicycle exercise was performed on a Dynavitt model 40 ergometer. The workload was started at 25 watts and increased by 25 watts every 3 minutes until exhaustion (dyspnea, fatigue or both). Heart rate and pulmonary and systemic pressures were assessed in the resting upright condition, in the last 30 seconds of each load level and at peak exercise; cardiac output was measured at upright rest and at peak exercise. During the exercise expiratory gases were collected to assess maximal oxygen consumption, carbon dioxide production and respiratory ratio by a system previously described. 15 A respiratory ratio >1 at peak exercise was

assumed as the proof of anaerobic metabolism, verifying a true maximal exercise.

Study protocol: The daily dose of digitalis and diuretics was kept constant throughout the study and was administered at 6:00 P.M. The study protocol is shown in Figure 1. The trial was conducted on 3 consecutive days: at 8:00 A.M. of each day, after basal resting hemodynamic measurements, a single oral dose of placebo or 40 or 60 mg of nicorandil was administered. The sequence of administration of the 3 preparations was randomized and double-blind: 3 patients followed the sequence (day 1, day 2, day 3) placebo-40 mg-60 mg, 3 patients the sequence 40 mg-60 mg-placebo and 3 patients the sequence 60 mg-placebo-40 mg. Parameter assessment was identical on each day and was as follows: supine resting hemodynamics were assessed at 8:00 A.M., just before drug administration, and then at 8:30, 9:00, 10:00, 11:00 A.M., 12:00 noon, 1:00 P.M., 2:00, 3:00 and 4:00 P.M.

Forearm blood flow and venous capacitance were assessed between 8:30 and 9:00 a.m. After 9:00 a.m. supine resting hemodynamic measurements were taken, patients were allowed to get on the cycloergometer, and after 5 minutes, resting upright hemodynamics were assessed. A symptom-limited exercise stress test was then performed as previously described. At the end of exercise, patients returned to bed for the subsequent resting hemodynamic measurements.

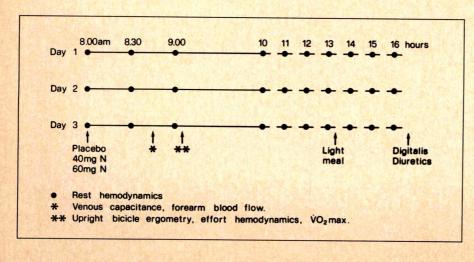


FIGURE 1. Study protocol.

Plasma samples for plasma renin activity and aldosterone were taken at 8:00 and 10:00 A.M. of each day and the assessment was made by radioimmunoassay. Plasma samples for catecholamines were taken at 8:00 and 9:00 A.M. of each day and the measurements were made by high pressure liquid chromatography using an electrochemical detector. Patients were allowed to have a standardized light meal after the 1:00 P.M. hemodynamics assessment.

**Data analysis:** Supine resting hemodynamic data were analyzed by Latin square analysis of variance for repeated observations. Upright resting and peak exercise hemodynamic data, forearm blood flow, venous capacitance and hormonal data were analyzed by Latin square analysis of variance. T tests were performed only if the F statistic was significant. A p value of <0.05 was considered statistically significant. Data are expressed as mean ± standard deviation.

# RESULTS

Baseline clinical characteristics of the 9 patients are listed in Table I. No differences were observed among the basal (8:00 A.M.) hemodynamic parameters of the 3 days of study.

When compared to placebo, peak supine resting hemodynamic effects of both doses of nicorandil were observed at 30 minutes (8:30) and 60 minutes (9:00). Table II lists supine resting and peak exercise hemodynamic data 60 minutes after dose (9:00). At rest, heart rate after both doses of nicorandil was unchanged. Mean blood pressure decreased by 9% after 40 and 60 mg of nicorandil and mean pulmonary artery pressure

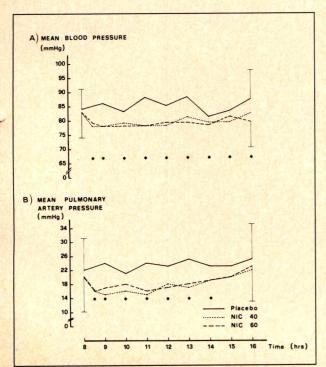


FIGURE 2. Time course of changes of mean blood pressure (A) and mean pulmonary pressure (B) after placebo, 40 mg and 60 mg of nicorandil (NIC) in 9 patients with congestive heart failure. \* p <0.05.

decreased by 37% after 40 mg and 29% after 60 mg of nicorandil. Mean pulmonary wedge pressure decreased by 40% after 40 mg and by 33% after 60 mg of nicorandil. Cardiac index was unchanged 60 minutes after both doses but was increased at 120 minutes (10:00) from  $2.6 \pm 0.5$  liters/min/m<sup>2</sup> after placebo to  $3.1 \pm 0.5$  liters/min/m<sup>2</sup> (p <0.05) after 60 mg and to  $2.9 \pm 0.7$  liters/min/m<sup>2</sup> (difference not significant) after 40 mg.

Systemic arteriolar resistance decreased 60 minutes after dose by 7% after 40 mg and by 13% after 60 mg of nicorandil. Pulmonary arteriolar resistance decreased by 32% after 40 mg and by 26% after 60 mg of nicorandil.

If we exclude cardiac indexes that increased significantly only after 60 mg of nicorandil, no differences were observed on peak supine resting hemodynamic effects between the doses of nicorandil. The time course of changes of supine resting hemodynamic parameters are shown in Figures 2 and 3. The reduction in mean blood pressure (Figure 2A) after both doses of nicorandil began at 30 minutes (8:30) and persisted significantly through 8 hours (4:00). No differences were observed between 40 and 60 mg of nicorandil. The reduction in mean pulmonary (Figure 2B) and wedge pressures (Figure 3A) began at 30 minutes (8:30) and persisted significantly through 7 hours (3:00) and 6 hours (2:00), respectively.

No differences were observed between 40 and 60 mg of nicorandil. Cardiac output (Figure 3B) increased significantly at 120 minutes (10:00), only after 60 mg, but in the subsequent measurements (11:00, 12:00 and

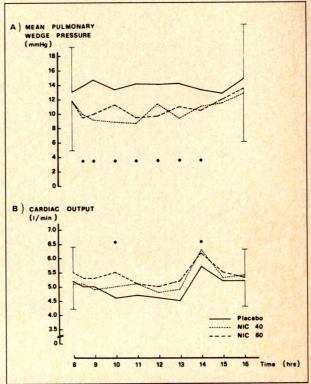


FIGURE 3. Time course of changes of mean pulmonary wedge pressure (A) and cardiac output (B) after placebo, 40 mg and 60 mg of nicorandil (NIC) in 9 patients with congestive heart failure. \* p <0.05.

TABLEII	Supine R	Supine Resting and Peak Exercise Hemodynamic	Peak Exe	rcise Hen	nodynamic		Data 60 Minutes After Dose	After Dose							
	HR		MBP		MPAP		MPWP		ਹ						
Patient	(beats/min)	min)	(mm Hg)		(mm Hg)		(mm Hg)		(liters/min/m²)	1/m²)	SAR (daing a nm-h)		VO <sub>2</sub> MAX	FBF	VC (ml)
No.	R	E	R	E	œ	E	8	E	R	E	R R	R R	(mil/min/kg) E	(mi/min/100g) R	R R
1P	72	130	88	110	14	30	6	25	3.3	6.5	1,408	80	26.2	4.3	5.8
8	82	140	80	103	00	20	4	11	2.9	6.4	1,435	72	30.9	4.3	5.8
09	78	120	82	80	6	17	2	14	3.2	6.5	1,309	65	25.5	53	28
2P	80	145	100	107	34	58	20	40	2.6	7.1	1,516	217	21.3	1.4	17
9	72	130	80	06	18	48	10	26	2.3	6.3	1,403	140	21.3	2.7	2.5
09	20	145	87	06	27	22	13	36	2.6	6.5	1,342	217	22.9	1.4	2.0
3P	98	152	92	117	40	29	24	37	3.7	5.3	1,074	198	15.5	2.7	3.3
8	75	135	75	103	26	29	15	27	3.6	5.6	932	176	17.1	2.9	4.4
9	82	155	75	113	25	70	15	36	3.7	5.7	930	161	17.8	2.8	3.8
4 P	75	130	11	98	15	20	6	29	3.6	4.9	066	99	16.2	2.2	2.8
4	81	130	11	97	8	46	2	21	2.9	5.5	1,019	30	18.4	2.5	3.3
9	72	140	89	93	14	54	8	27	3.6	5.7	837	77	19.1	3.0	3.0
5P	8	135	87	11	25	40	14	25	2.9	5.2	1,336	171	17.5	3.8	2.6
49	8	125	70	83	21	25	===	18	3.3	6.4	940	136	15.8	4.2	3.7
9	8	1	20	1	6	1	2	1	3.2	1	686	57	1	2.6	2.9
6P	75	128	8	11	32	46	17	24	2.1	4.0	1,596	299	23.5	0.5	1.5
4	78	150	78	95	14	46	10	32	1.9	5.6	1,612	83	22.1	0.7	1.9
99	74	155	78	95	21	22	10	30	2.3	4.9	1,393	193	21.3	1.0	2.2
7 P	2	115	83	97	13	28	7	16	2.8	5.5	1,401	101	22.9	1.8	3.8
9	72	1	82	1	13	1	80	1	3.3	1	1,137	70	1	1.6	2.4
09	72	110	82	103	15	30	<b>∞</b>		3.3	7.8	1,171	100	25.1	2.4	2.8
8P	78	175	87	93	<b>&amp;</b>	38	2		2.9	5.1	1,540	53	24.3	7.9	3.1
9 :	88	180	8	100	2	36	2		2.8	5.4	1,611	55	24.2	7.1	4.4
9 60	92	185	87	103	<b>&amp;</b>	35	9		3.3		1,357	31	27.4	8.9	2.5
9.6	85	150	83	87	32	33	26		2.4	2.9	1,585	115	10.7	1.3	1.4
9 :	83	155	75	97	20	40	14		2.3	4.0	1,511	121	12.2	1.8	1.9
09	06	158	11	82	22	30	19		2.3	2.9	1,499	58	6.6	1.3	1.0
Mean ± SD P	79 ± 7	139 ± 18	86±7	95±14		45±13	+	29 ± 8	₹ 6	5.4±0.9	1,382 ± 218	144 ± 82	19.8 ± 5.1	2.9 ± 2.3	2.9 ± 1.4
04	9∓8/	143±18	78±7*	2 ₹ 96	15 ± 7*	43 ± 14	+	24 ± 7*	2.8 ± 0.6	5.7 ± 0.6	1,289 ± 282*	98 ± 47*	20.2 ± 5.7	3.1 ± 1.9	3.4 ± 1.3
09	80∓ <sub>9</sub>	142 ± 24	78±7*	94 ± 12	17 ± 7*	46±18	10 ± 5*	27 ± 8	$3.1 \pm 0.5$	5.9 ± 1.1	1,207 ± 226*	107 ± 67*	$21.1 \pm 5.6$	3.0 ± 1.9	2.6 ± 0.8
* p <0.05 vs pl	acebo. tp =	0.1 vs placebo.	- forman	lood flour.		001								* p <0.05 vs placebo. † p = 0.1 vs placebo.	
= supine rest; SA	R = systemik	c arteriolar resignation	stance; SD =	standard de	eviation; VC =	venous capa	citance; VO2	MAX = maxir	= mean puim	onary artery pri	essure; MPWP = mea	an pulmonary wedge pre	essure; P = placebo; I	PAR = pulmonary arteri	olar resistance; R
									,		0	i francodos i impreso	Her doller.		

1:00) the difference was no longer statistically significant. The physiologic increase in cardiac output after the meal (eaten after the 1:00 P.M. measurements) was observed at the 2:00 P.M. measurement and cardiac output was statistically higher after 40 mg (6.3  $\pm$  1.5 liters/min, p <0.05) and 60 mg (6.2  $\pm$  1.0 liters/min, p <0.05) of nicorandil than after placebo (5.7  $\pm$  1.0 liters/min). There were no statistically significant effects of nicorandil on resting forearm blood flow (Table II). Forearm venous capacitance (Table II) increased, though not significantly, by 15% (p = 0.1) after 40 mg of nicorandil and was unchanged after 60 mg.

At peak exercise there were no statistically significant effects of nicorandil on heart rate, mean blood pressure, mean pulmonary pressure, cardiac index and maximal oxygen consumption. Mean pulmonary wedge pressure was reduced by 17% after 40 mg of nicorandil and was unchanged after 60 mg. Plasma renin activity increased from 19.4 ± 32 mg/ml/hour after placebo to  $30.4 \pm 33$  ng/ml/hour (p < 0.05) after 40 mg and to 27.4 ± 37 (p <0.05) after 60 mg of nicorandil. Plasma aldosterone (756  $\pm$  576 pg/ml after placebo, 836  $\pm$  398 and 838 ± 492 pg/ml after 40 and 60 mg of nicorandil), epinephrine (25  $\pm$  19 pg/ml after placebo, 33  $\pm$  28 and 33  $\pm$  19 pg/ml after 40 and 60 mg of nicorandil) and norepinephrine (124 ± 90 pg/ml after placebo, 144  $\pm$  94 and 150  $\pm$  84 pg/ml after 40 and 60 mg of nicorandil) were normal at baseline and tended to be increased, though not significantly, after both doses of nicorandil compared to placebo. Two patients after placebo, 2 after 40 mg and 4 after 60 mg of nicorandil had headaches, while 1 patient after placebo, 2 after 40 mg and 2 after 60 mg of nicorandil had symptomatic orthostatic hypotension and in 2 cases the upright exercise test was prevented (Table II). Another patient, who was not included in this study, developed severe symptomatic hypotension 30 minutes after 60 mg of nicorandil; the patient was considered a dropout.

# **DISCUSSION**

This double-blind, randomized, placebo-controlled trial demonstrates that nicorandil produces favorable hemodynamic effects in patients with CHF. Single oral doses of 40 and 60 mg of nicorandil decrease supine resting mean blood pressure, mean pulmonary artery and wedge pressures and systemic and pulmonary resistances up to 6 to 8 hours. Our results demonstrate that nicorandil exerts an unloading action on the failing heart and induces an improvement in cardiac pump function. The reduction of preload was greater than the decrease of afterload and the hemodynamic effects of nicorandil were very similar to the effects of the orally administered nitrates in CHF.16 Only after the 60-mg dose of nicorandil was a transient and slight increase in supine resting cardiac output observed. On the other hand, the mean basal cardiac index of our patient population was normal at rest (Table II) and in this setting the reduction of the afterload induced by nicorandil cannot increase the cardiac output to a great extent. Solal et al<sup>17</sup> reported a 55% increase in resting cardiac output with similar doses of nicorandil, but their pa-

tients had more severe CHF, with lower cardiac index and higher pulmonary wedge pressure.

More interesting is the observation that the cardiac output after the meal was statistically higher after 40 and 60 mg of nicorandil than after placebo (Figure 4). Hemodynamic changes after meals in patients with CHF include an increase in heart rate and cardiac index and a reduction in peripheral resistance. 18,19 In a previous trial of patients with CHF we observed that short- and long-term treatment with captopril restored the postprandial increase in cardiac output that was very small after placebo.20 The mechanisms underlying these effects may be related to the improvement in cardiac performance induced by vasodilator drugs that produces a more physiologic hemodynamic response to

While both doses of nicorandil produced no change in resting forearm blood flow, only after 40 mg did we observe an increase in forearm venous capacitance that was of borderline statistical significance (p = 0.1) (Table II). Analysis of this behavior of venous capacitance in single patients (Figure 4) shows that after 40 mg an increase was observed in 8 of 9 cases while after 60 mg an increase was observed in 5 cases and a decrease in 4 cases. Conflicting results have been obtained by different investigators on the effects of nicorandil on venous return and venous capacitance. 1,21-24 Our data show that the effects of nicorandil on venous return appear to be less pronounced than those of classic nitrates and, in single patients, may be easily counterbalanced by the baroreceptor reflex triggered by hypotension, mainly

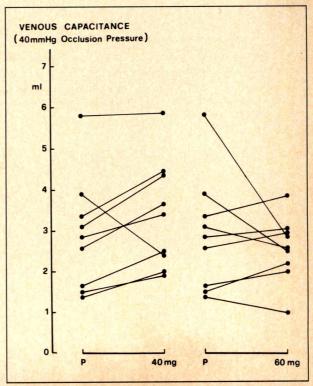


FIGURE 4. Venous capacitance 45 minutes after administration of placebo (P), 40 and 60 mg of nicorandil in 9 patients with congestive heart failure.

with the higher dose of the drug. Peak exercise hemodynamic data (Table II) show a decrease in mean pulmonary wedge pressure only after the 40-mg dose of nicorandil and this effect may be consistent with the more evident action on venous capacitance of the smaller dose.

Since the magnitude and the time course of the rest hemodynamic data are virtually identical after the 2 doses of nicorandil, the effects on venous capacitance and on peak exercise hemodynamics indicate that 40 mg of nicorandil 3 times daily may be the dose of choice in patients with CHF.

Orthostatic symptomatic hypotension has been a true clinical problem, necessitating prolonged supine rest in 2 of 9 patients after 40 mg and in 3 of 10 patients after 60 mg.

Postural hypotension was induced only by the first administration of the drug, regardless of the dose. Patients who experienced hypotension after 40 mg of nicorandil had no symptoms when the second dose was 60 mg. The reverse was also true.

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# Follow-Up in Mitral Valve Prolapse by Phonocardiography, M-Mode and Two-Dimensional Echocardiography and Doppler Echocardiography

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To assess the serial phonocardiographic and echocardiographic change in patients with mitral valve prolapse (MVP), phonocardiograms and echocardiograms were reviewed retrospectively in 116 patients (48 men and 68 women, mean age 27 years) who had been determined to have MVP and were reexamined 4.3 years (range 1 to 14) later by phonocardiography and echocardiography between 1971 and 1988. Follow-up phonocardiograms showed periods when 5 of 18 patients with silent MVP developed mid- or late systolic clicks. Of 57 patients with mid- or late systolic clicks, 15 had silent MVP, 6 developed a late systolic murmur with or without systolic clicks and 1 developed a pansystolic murmur. Two of 9 patients with an isolated late systolic murmur developed a pansystolic murmur. M-mode echocardiograms showed that left atrial and left ventricular dimensions at end-diastole and end-systole increased in patients with systolic murmur (33  $\pm$  10 vs 35  $\pm$  11, 46  $\pm$  6 vs 50  $\pm$ 7 and 29  $\pm$  4 vs 31  $\pm$  5 mm, respectively, all p <0.001) and no statistically significant changes in any of these dimensions were found in patients without a systolic murmur. The degree of MVP evaluated by the anteroposterior mitral leaflet angle on the 2-dimensional echocardiogram was more severe in patients with a systolic murmur than in patients without systolic murmur (157  $\pm$  12 vs 131  $\pm$  16°, p <0.001). The degree of prolapse did not change during the follow-up periods. The number of patients with mitral regurgitation detected by pulsed Doppler echocardiography increased from 21 of 72 (29%) to 31 of 72 (43%). The present study suggests that the systolic murmur confirmed by phonocardiography should be taken into consideration in evaluating severity and in assessing prognosis of MVP.

(Am J Cardiol 1990;65:349-354)

Reid¹ and Barlow et al² recognized the relation between midsystolic click and mitral valve abnormality >20 years ago. Left ventriculography was subsequently used to disclose billowing of the mitral valve into the left atrium and consequent mitral regurgitation. It was the advent of echocardiography that led to widespread recognition of mitral valve prolapse (MVP) as a common cardiovascular abnormality, the incidence of which is 1 to 24%.³-7 Although several investigators have evaluated serial auscultatory or echocardiographic changes in patients with MVP,8-11 few performed follow-up studies of patients with MVP by both phonocardiography and echocardiography. This study was undertaken to observe the serial phonocardiographic and echocardiographic changes in patients with MVP.

# **METHODS**

Study population: A total of 116 patients phonocardiographically or echocardiographically determined to have MVP were reexamined at least once after the initial study by phonocardiography and echocardiography between 1971 and 1988 in the Second Department of Internal Medicine, University of Tokyo. Of 116 patients, 48 were men and 68 were women, and their mean age was 27 ± 18 (standard deviation) years (range 7 to 81). The diagnosis of MVP was based on the presence of at least one of these findings: mid- or late systolic click at rest or provoked by amyl nitrite or methoxamine or late systolic murmur at rest or provoked by amyl nitrite or methoxamine on the phonocardiogram, midsystolic buckling or pansystolic bowing of ≥3 mm in depth recorded from the midintercostal space on M-mode echocardiogram or systolic protrusion of the mitral valve leaflet beyond the mitral valve ring on the 2-dimensional echocardiogram. 12,13 Patients with MVP were excluded from the study if they had a history of rheumatic fever or rheumatic heart disease, coronary artery disease, primary or secondary cardiomyopathy, congenital heart diseases, connective tissue diseases (including Marfan syndrome) or hyperthyroidism.

The original phonocardiograms and echocardiograms were retrospectively reviewed for the recognition of click and systolic murmur on the phonocardiogram, the measurement of intracardiac dimensions on the M-mode echocardiogram, the assessment of the degree of MVP on the 2-dimensional echocardiogram and the

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evaluation of mitral regurgitation on the pulsed Doppler flow velocity tracing.

Assessment of the degree of mitral valve prolapse: To assess the echocardiographic degree of MVP, videotape recordings of 2-dimensional echocardiograms were reviewed, and the parasternal long-axis image of the left ventricle was selected and frozen in late systole. On the

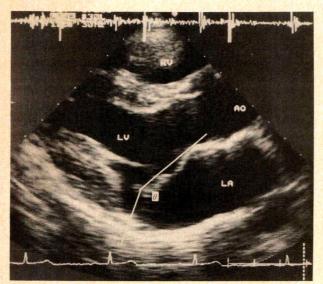


FIGURE 1. Measurement of the anteroposterior mitral leaflet angle  $(\theta)$ . AO = aorta; LA = left atrium; LV = left ventricle; RV = right ventricle.

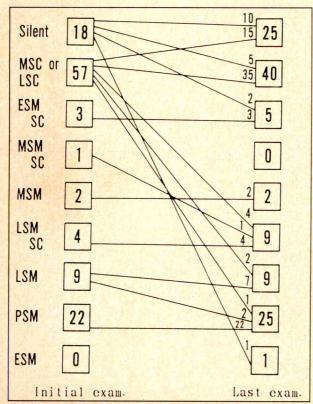


FIGURE 2. Phonocardiographic findings in the initial and last examinations. C = click; E = early; LS = late systolic; M = murmur; MS = midsystolic; PS = pansystolic; S = systolic; Silent = silent mitral valve prolapse.

frozen image, 2 lines were drawn from the leaflet coaptation point, one to the junction of the posterior aortic wall and aortic cusp, and another to the posterior mitral anulus. Then the angle between the 2 lines was measured as shown in Figure 1. The measurement was made in 3 beats for each examination, and the average value was calculated.

**Statistical methods:** All data are presented as mean  $\pm 1$  standard deviation; paired or unpaired Student t tests were used for the quantitative paired or unpaired data.

# RESULTS

Clinical findings: The mean follow-up period was 4.3 ± 2.7 years (range 1 to 14). Of 116 patients, 101 were asymptomatic at the initial study. The main reasons for the initial examination were the abnormal auscultatory findings such as clicks and murmurs in 78 patients, electrocardiographic abnormalities in 8 and the further evaluation of known MVP in 15. Of these 101 patients, 2 patients developed palpitations, 3 developed dyspnea and 1 developed chest pain during follow-up. In the remaining 15 patients, 5 had dyspnea, 9 had palpitations and 1 had chest oppression at the initial examination. The symptoms disappeared in 4 patients at the time of reexamination.

Phonocardiographic findings: Figure 2 shows the changes in the phonocardiographic features found between the initial and last examinations. Five of 18 patients with silent MVP developed mid- or late systolic clicks, 2 developed an early systolic murmur associated with systolic clicks, 1 developed an early nonejection systolic click and no changes were found in the other 10 patients. Of 57 patients with mid- or late systolic clicks, 15 lost clicks (silent MVP), 4 developed a late systolic murmur with systolic click, 2 an isolated late systolic murmur and 1 a pansystolic murmur, and the other 35 patients showed no change. The midsystolic murmur with click in 1 patient became a late systolic murmur with systolic click at the last examination. Two of 9 patients with an isolated late systolic murmur developed a pansystolic murmur (Figure 3), and the other 7 patients showed no change. None of 22 with pansystolic murmur, 3 with early systolic murmur with systolic click, 2 with midsystolic murmur or 4 with late systolic murmur with systolic click showed any change.

Intracardiac dimensions (M-mode echocardiography): Serial measurements of left atrial, left ventricular end-diastolic and left ventricular end-systolic dimensions were available in 111 patients. Values for the left atrial dimension from the initial and last studies were  $28 \pm 8$  and  $29 \pm 9$  mm, the left ventricular end-diastolic dimension  $44 \pm 6$  and  $45 \pm 7$  mm and left ventricular end-systolic dimension  $27 \pm 5$  and  $28 \pm 6$  mm. None of these changes was statistically significant. However, when the patients were divided into 2 groups according to the presence or absence of systolic murmur, the left atrial dimension increased from  $33 \pm 10$  to  $35 \pm 11$  mm (p <0.001), left ventricular end-diastolic dimension from  $46 \pm 6$  to  $50 \pm 7$  mm (p <0.001) and left ventric-

ular end-systolic dimension from  $29 \pm 4$  to  $31 \pm 5$  mm (p < 0.001) in 45 patients with systolic murmur (including early systolic murmur, midsystolic murmur, late systolic murmur and pansystolic murmur). In contrast, statistically significant changes were not found in any left atrial (25 ± 4 to 25 ± 4 mm), left ventricular enddiastolic (41 ± 6 to 42 ± 6 mm) or left ventricular endsystolic dimension (25  $\pm$  5 to 26  $\pm$  4 mm) in 66 patients without systolic murmur (Figure 4).

Degree of mitral valve prolapse (two-dimensional echocardiography): Serial measurements of the anteroposterior leaflet angle were obtainable in 53 of 99 (53%) patients. In the initial examination, the angle in 23 patients with systolic murmur was larger than in those without systolic murmur (157 ± 12 vs 131 ± 16°, p <0.001, Figure 5), indicating more severe degree of MVP in the former group. However, the changes in the angle between the initial and last studies were not statistically significant (p > 0.05) in patients with (157  $\pm$  12 and 155  $\pm$  11°) or without (131  $\pm$  16 and 133  $\pm$  14°) systolic murmur (Figure 6).

Mitral regurgitation (pulsed Doppler echocardiography): Follow-up pulsed Doppler echocardiographic examination was performed in 72 patients. Initial examination revealed mitral regurgitation in 21 patients. Of them, 9 patients had late systolic murmur, 11 had pansystolic murmur and 1 had no systolic murmur. In 51 patients without mitral regurgitation, 6 had late systolic murmur and 45 had no systolic murmur.

The last pulsed Doppler echocardiographic examination showed new mitral regurgitation in 10 of the 51 patients. Meanwhile, the initial and last phonocardiographic examinations showed an evolution of a late systolic murmur with or without systolic clicks from midor late systolic clicks in 4 of these 10 patients. Thus, the incidence of mitral regurgitation increased from 21 of 72 (29%) to 31 of 72 (43%) during the follow-up peri-

# DISCUSSION

Previous follow-up studies of MVP were mainly focused on its long-term prognosis and complications, 14-17 but not on its serial changes of phonocardiographic and echocardiographic findings. In this study, we observed the evolution of phonocardiographic features and Mmode, 2-dimensional and Doppler echocardiographic findings in 116 patients with MVP over a mean of 4.3 years.

Phonocardiographic changes: Midsystolic clicks and late systolic murmurs have been considered diagnostic hallmarks of MVP2,18-21 and were reported to be present in 82 to 100% of patients with MVP.20,22 Our follow-up phonocardiographic examination revealed these features in 83 of 116 (71%) patients. In the remaining 33 patients, 7 patients exhibited an early or midsystolic murmur. These findings are also considered to be the auscultatory sign of this condition. 20,23

The substantial proportion (5 of 18) of patients with silent MVP on initial examination exhibited typical clicks on follow-up in the present study. This suggests that the distinction between phonocardiographically silent and expressed MVP is not as stable as implied in many reports based on single evaluation, and that echocardiography is a sensitive and reliable method in diagnosing MVP.

In this study, the disappearance of systolic murmurs was not encountered between the initial and last phonocardiographic examinations. This finding was not in accord with previous reports based on auscultation in which 27 to 69% of subjects who had systolic murmur

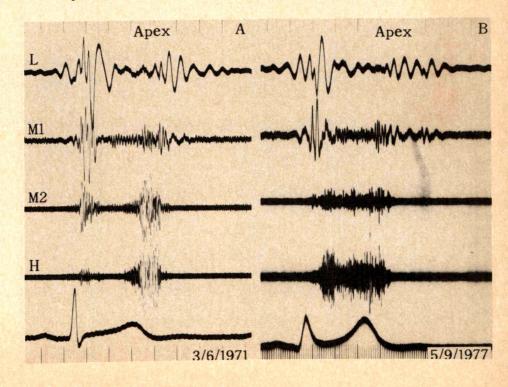


FIGURE 3. Phonocardiograms in a 34-year-old man who first demonstrated a late systolic murmur (A), but 6 years later showed a par systolic murmur (B).

(mainly late systolic murmur) on initial auscultation did not exhibit any kind of systolic murmurs on the followup auscultation after 4 years. 22,24,25 This discrepancy may be partially explained by the method by which the systolic murmur was detected.

The present study revealed that in 2 patients who had a late systolic murmur on the initial examination, a pansystolic murmur developed during the follow-up period. This finding was compatible with the hypothesis that mitral regurgitation gradually progresses in severity in a subset of patients with MVP.16

Echocardiographic change: A statistically significant increase in left atrial and ventricular dimensions was noted between the initial and last echocardiographic examination in patients with systolic murmur, but not in patients without systolic murmur. In the present and previous studies, 26-28 the percentage of mitral regurgitation detected by Doppler echocardiography in MVP patients with systolic murmur was much higher than that in MVP patients without systolic murmur, and the sig-

nificant mitral regurgitation could only be detected by pulsed Doppler echocardiography in MVP patients with holosystolic murmur. Therefore, we speculate that the progressive increase in left atrial and ventricular dimensions in patients with systolic murmurs is mainly due to mitral regurgitation. In patients with MVP diagnosed by M-mode echocardiography, Devereux et al11 reported that there was no change in any left atrial or left ventricular dimensions during short-term follow-up (5 to 18 months) and the left atrium increased in size only during longer follow-up (19 to 54 months). Kolibash et al10 also found a significant increase in left atrial size evaluated by echocardiography in 11 MVP patients with systolic murmur over a mean 2-year interval. These studies suggested that the change in intracardiac dimensions seems to depend on the length of the followup period.

In this study, the anteroposterior leaflet angle was used as an index of the degree of MVP and was larger in MVP patients with systolic murmur than in those

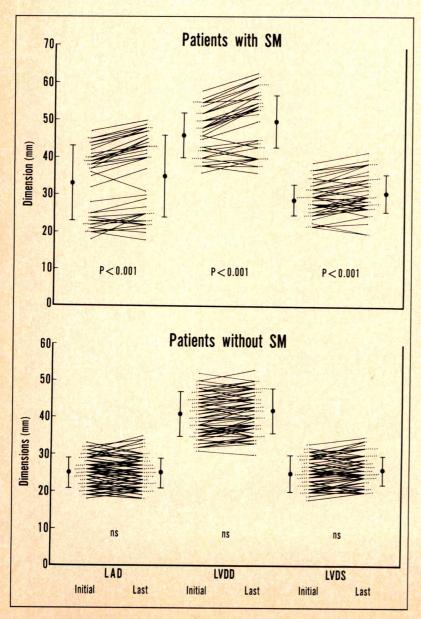


FIGURE 4. The initial and last M-mode echocardiographic measurements of intra cardiac dimensions in patients with (top) and without (bottom) systolic murmur (SM). LAD = left atrial dimension; LVDD left ventricular end-diastolic dimension; LVDS = left ventricular end-systolic dimension; ns = statistically not significant.

P < 0.001

180

170

160

150

1 140

1 130

1 100

90

80

80

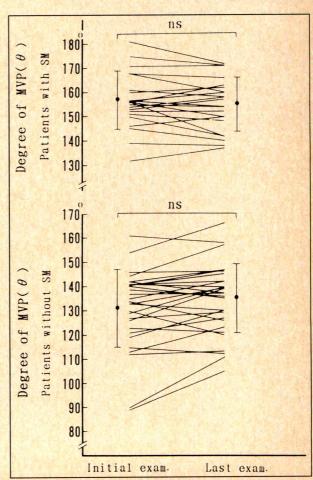
Patients with SM

FIGURE 5. Measurements of the degree of mitral valve prolapse (MVP) assessed by the antero-posterior mitral leaflet angle  $(\theta)$  in patients with and without systolic murmur (SM).

without systolic murmur. The methods used by us and other investigators<sup>29-31</sup> are based on the same principle; the more severe the superior systolic displacement of leaflet coaptation point, the more severe the degree of MVP. Sunami et al<sup>31</sup> used the same anteroposterior angle as an index for evaluating MVP and found a larger angle in patients with MVP than normal persons. Krivokapich et al<sup>29</sup> also disclosed a markedly superiorly displaced coaptation point in 91% of patients with MVP with holosystolic murmur.

The degree of MVP itself did not show statistically significant progress in either group of patients with or without systolic murmur. Furthermore, it even showed a tendency to regress in some patients with systolic murmur. It is believed that MVP results from a valvular-ventricular disproportion.<sup>32</sup> We speculate that the decrease in the degree of MVP in some patients with systolic murmur may be due to an increase in the left ventricular dimension and related to the secondary scaring fibrosis of chordae and leaflets, as observed in some autopsy studies.<sup>33,34</sup> Devereux et al<sup>11</sup> also found a decrease in the depth of prolapse on M-mode echocardiograms in patients with MVP on 2 occasions separated by 19 to 54 months.

Our initial pulsed Doppler echocardiographic examination detected mitral regurgitation in 21 of 72 (29%) patients with MVP. This finding is in agreement with previous studies<sup>26–28</sup> that reported that the prevalence of mitral regurgitation detected by pulsed Doppler echocardiography is high in patients with echocardiographic evidence of MVP. In the last examination, mitral regurgitation was newly detected in 10 patients. This may be explained in part by the advanced technology in recent years, in which the pulsed Doppler echocardiographic examination was performed under the guidance of color-coded Doppler flow imaging.



Patients without

FIGURE 6. Measurements of the degree of mitral valve prolapse (MVP) assessed by the antero-posterior mitral leaflet angle  $(\theta)$  at the initial and last examinations in patients with (top) and without (bottom) systolic murmur (SM). ns = statistically not significant.

A previous study<sup>22</sup> suggested that the incidence of complications in patients with MVP parallels auscultatory evidence of the severity of mitral regurgitation. The present retrospective follow-up study showed a statistically significant increase in left atrial and left ventricular dimensions during follow-up periods in patients with systolic murmur, and a more severe degree of prolapse and a higher incidence of mitral regurgitation in patients with systolic murmur than in those without it. Thus, systolic murmur, especially when confirmed by phonocardiography, should be taken into consideration in evaluating severity and in assessing prognosis of

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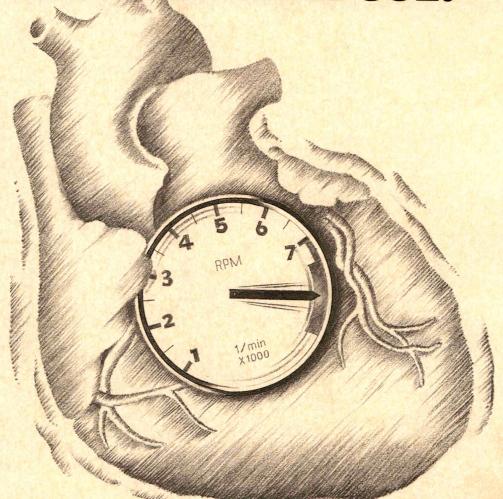
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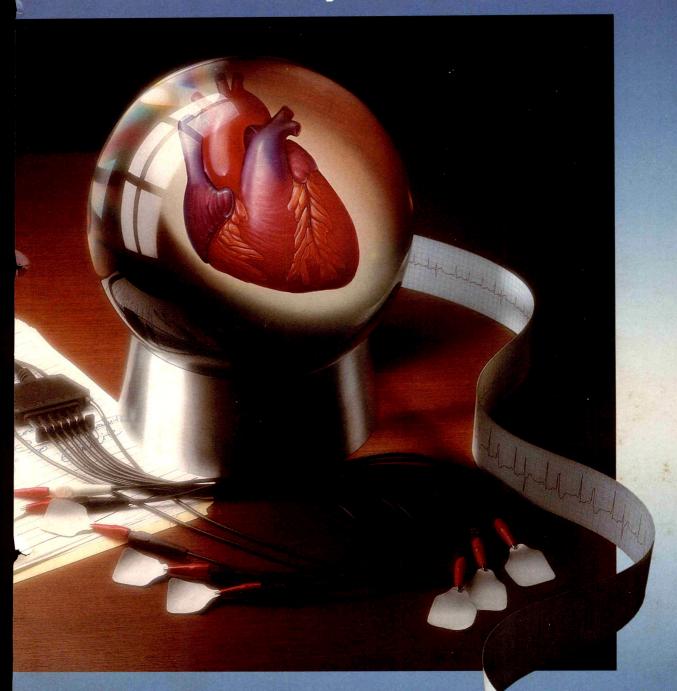
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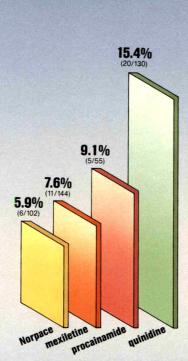
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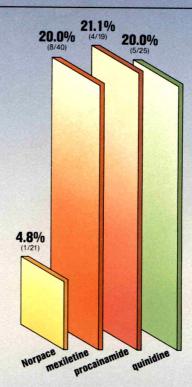
# **Predictability, short-term**

Clinical studies have found Norpace\* (disopyramide phosphate) to have a low incidence of proarrhythmia.<sup>12</sup>

Frequency of aggravation of arrhythmia among selected agents tested<sup>1,2</sup>



Adapted from Velebit et al.<sup>1</sup>
Results based on noninvasive testing.



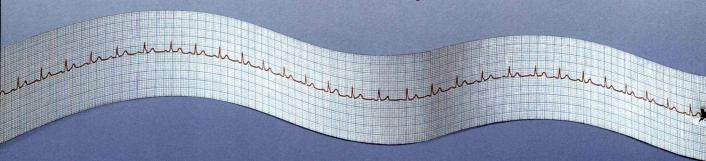
Adapted from Poser et al.<sup>2</sup> Results based on invasive testing.

# **Predictable side effects**

Norpace CR is generally well tolerated. The side effects are usually dose-related and generally not a cause for drug withdrawal in well-chosen patients.<sup>3</sup>

The most commonly seen side effects of disopyramide phosphate are anticholinergic, and the most severe are due to its negative inotropic properties.

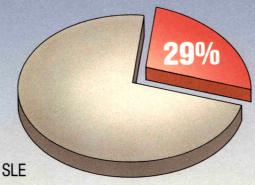
Disopyramide is contraindicated in patients with a history of cardiogenic shock, preexisting second-or third-degree AV block (if no pacemaker is present), congenital Q-T prolongation, or known hypersensitivity to the drug.



# **Predictability, long-term**

Norpace (disopyramide phosphate) is rarely associated with late-appearing toxicities such as lupus and agranulocytosis.<sup>4</sup>

# Incidence of lupus (SLE\*) with procainamide 5



Adapted from Henningsen et al.5

During a five-year follow-up study, 29% (12/42) of patients developed a classic drug-induced SLE syndrome.<sup>5</sup> Additional studies confirm this frequent adverse reaction.<sup>4,6</sup>

\*Systemic lupus erythematosus.

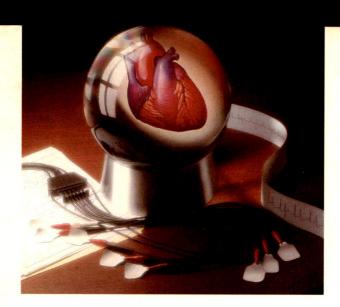
# Results of a long-term follow-up (up to 64 months) of patients on Norpace (disopyramide phosphate):

- In 60% (24/40) of patients, Norpace provided effective and tolerated monotherapy for up to 64 months.<sup>7</sup>
- Anticholinergic side effects, although common, were usually tolerated.<sup>7</sup>

Predictable therapy

100-mg and 150-mg CAPSULES

NORPACE CR B.I.D (disopyramide phosphate extended-release)



# Predictable therapy

100-mg and 150-mg CAPSULES OR**PACE** CR B.I.D. (disopyramide phosphate extended-release)

# Predictable monotherapy

· Effective first-line antiarrhythmic control comparable to that of quinidine.8

# Predictability, short-term

- Side effects are usually manageable.
- Not generally associated with hypersensitivity reactions.
- Low incidence of proarrhythmia.<sup>2,4</sup>

# Predictability, long-term

- Few late-appearing adverse reactions such as lupus or agranulocytosis.
- Low drop-out rate as compared with auinidine.8
- Established safety profile through 12 years

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# Norpace® Capsules

(disopyramide phosphate)

# Norpace® CR Capsules

(disopyramide phosphate extended-release)

# **Brief Summary**

Before prescribing, please consult current complete prescribing information, a summary of which follows: Indications: For suppression and prevention of recurrence of the following cardiac arrhythmias: unifocal premature (ectopic) ventricular contractions; premature cardiac arrnythmiss, unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with DC-cardioversion). Norpace is equally effective in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease. Norpace CR should not be used initially if rapid establishment of disopyramide placema layels is desired. Clad disopyramide hopeshate has not been adequately studie in ordinarily treated with DC-cardioversion). Norpace is equally effective in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary arreyy diseases. Norpace CR should not be used initially if apid establishment of disopyramide plasma levels is desired. Oral disopyramide phosphate has not been adequately studied in patients with acute myocardial infraction or with persistent ventricular tachycardia or atrial arrhythmic drugs in preventing sudden death in patients with serious ventricular activity as not been established. Contraindications: Cardiogenic shock, previsting second- or third-degree AV block (if no pacemaker is present), congental Q-T prolongation, or known hypersensitivity to the drug. Warnings. Norpace or Norpace CR may cause or worsen congestive heart failure (CHF) or produce severe hypotension as a consequence of its negative inotropic properties. Hypotension has been observed primarily with primary cardiomyopathy or inadequately compensated CHF or hypotension unless the condition is secondary to cardiac arrhythmia. Patients with a history of heart failure may be treated with Norpace or Norpace CR, should not be used in patients with a patients. With Norpace or Norpace CR, but careful attention must be given to maintaining cardiac function, including optimal digitalization. If hypotension occurs or CHF worsens, Norpace or Norpace CR should be discontinued and, if necessary, restarted at a lower dosage only after adequate cardiac compensation has been established. Norpace or Norpace CR should be discontinued and, if necessary, restarted at a lower dosage only after adequate cardiac compensation has been established. Norpace or Norpace CR should be discontinued in significant widening (greater than 25%) of the QRS complex occurs. Patients with however the patients with Norpace or Norpace CR with other Type 1 antiarrhythmic drug must be carefully monitored. If fi pregnancy has not been established. Disopyramide has been found in human fetal blood.

Norpace has been reported to stimulate contractions of the pregnant uterus. Use of Norpace or Norpace CR in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus. Effects of Norpace or Norpace CR on the fetus during delivery or on the course of labor and delivery are unknown. Following oral administration, disopyramide has been found in human milk at a concentration not exceeding that in plasma. Because of the potential for serious adverse reactions in nursing infants from Norpace or Norpace (R, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. Adverse Reactions: Dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention especially in males with benign prostatic hypertrophy, urinary frequency and urgency, impotence, nausea, pain/bloating/gas, anorexia, diarrhea, vomiting, nervousness, dizziness, general fatigue/muscle weakness, headache, malaise, aches/pains, hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain, generalized rash/dermatoses, itching, hypokalemia, elevated liver cholesterol/triglycerides, depression, insomnia, dysuria, numbness/tingling, elevated liver cholesterol/triglycerides, depression, insomnia, dysuria, numbness/tingling, elevated liver enzymes, AV block, elevated BUN, elevated creatinine, decreased hemoglobin/hematocrit, enzymes, AV block, elevated BUN, elevated creatinine, decreased hemoglobin/hematocrit, and hypoglycemia. Acute psychosis, cholestatic jaundice, and agranulocytosis, all three reversible, have been reported, as have fever, respiratory difficulty, thrombocytopenia, an gynecomastia. Some cases of lupus erythematosus (LE) symptoms have occurred, mostly patients switched from procianamide to disopyramide following the development of LE symptoms. Dosage and Administration: Dosage must be individualized on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg/day given in divided doses: q8h for Norpace and q12h for Norpace CR. See current complete prescribing information for dosage recommendations.

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# In Vivo Identification of Mitral Valve Fibrosis and Calcium by Real-Time Quantitative Ultrasonic Analysis

Fabio Lattanzi, MD, Eugenio Picano, MD, Luigi Landini, PhD, Alessandro Mazzarisi, Gualtiero Pelosi, MD, Antonio Benassi, PhD, Leonardo Salvatore, MD, Alessandro Distante, MD, and Antonio L'Abbate, MD

Conventional echocardiography provides fundamental information about mitral valve morphology and function but has a relatively low specificity in evaluating valve calcific deposits, which is critical information for the preoperative decision to perform commisurotomy or replacement. In vitro radiofrequency ultrasonic quantitative analysis of the mitral valve has been demonstrated to be a reliable tool in identifying normal, fibrotic and calcific valves. This study evaluates quantitative ultrasound characterization of the mitral valve in vivo. Thirtythree patients, scheduled to undergo mitral valve replacement, and 20 normal subjects (10 young and 10 older control subjects) were studied with a 2.25-MHz transducer. Radiofrequency signal was analyzed by a microprocessor system (used with an M-mode commercially available echocardiograph) for on-line evaluation of ultrasonic backscatter with 8 bits of amplitude resolution, 40-MHz sampling rate and a 1-µs acquisition gate. The integrated value of the rectified radiofrequency signal amplitude was deemed the integrated backscatter index. The highest value recorded with the ultrasonic analysis from each valve was taken as representative and expressed as the percent value with respect to the pericardial integrated backscatter index value of that subject. The 33 excised mitral valves underwent histologic examination. Four groups were identified: young controls (group I, n = 10); older controls age-matched with patients (group II, n = 10); patients with fibrotic mitral valves (group III, n = 13); and patients with calcific mitral valves (group IV, n = 20). A statistically significant (p <0.01) difference was found among the 4 groups for the percent integrated backscatter index: group I 5  $\pm$  2, group II 8  $\pm$  4 (p <0.05 vs group I), group III 17  $\pm$  9 and group IV 52  $\pm$  30. In conclusion, a microprocessor-based system for online evaluation of radiofrequency ultrasonic signal is able to differentiate normal, fibrotic and calcific mitral valves in vivo.

(Am J Cardiol 1990;65:355-359)

ecently, quantitative ultrasound analysis by means of nonconventional parameters has been demonstrated to be feasible and reliable in characterizing cardiovascular structures. 1,2 We have shown that quantitative radiofrequency evaluation of backscattered echo is able to identify different degrees of mitral valve pathologic impairment in vitro.3 The echocardiograph used for on-line mitral valve in vitro analysis in our institution was used in the in vivo setting.4,5 Previous reports have shown the feasibility and reproducibility of in vivo measurements of the radiofrequency ultrasound signal.<sup>5,6</sup> Therefore, the next logical step is the evaluation, by means of the same ultrasound system, of patients with mitral valve disease. This study was intended to verify the usefulness of an echocardiographic system—using a relatively simple quantitative parameter based on ultrasonic backscatter-in differentiating in vivo normal, fibrotic and calcific mitral valves.

#### **METHODS**

Patient population: Thirty-three in-hospital patients (9 men, 24 women; mean age 62 ± 14 years) were evaluated. All were scheduled to undergo surgery for mitral valve replacement; all were symptomatic and had a baseline Doppler echocardiogram clearly diagnostic for mitral valve stenosis (15 patients), regurgitation (8) or both (10). Etiology and characteristics of mitral valve disease for each patient are listed in Table I. A control group of 10 subjects (5 men and 5 women; mean age 27 ± 4 years) was also studied. They were all asymptomatic and had a normal physical examination, routine electrocardiogram and echocardiogram. The values of ultrasonic quantitative analysis obtained from the mitral valves of these subjects were used as normal reference values. Finally, a control group of 10 older patients (4 men, 6 women; age 62 ± 6 years), age-matched with patients with mitral valve disease, was included in the study. They were also asymptomatic and had normal electrocardiogram and echocardiogram; in particular, their mitral valve leaflets, by conventional qualitative echocardiography, showed normal thickness and texture. This group was studied to evaluate the difference in mitral backscatter among age-matched populations, but it cannot be considered a true control group, because older subjects, even though asymptomatic and with normal echocardiographic appearance, have a certain degree of mitral valve degeneration and an increase in fibrotic content should be present.

From the Consiglio Nazionale delle Ricerche Clinical Physiology Institute and the Cardiothoracic Surgery Division, University of Pisa, Pisa, Italy. Manuscript received May 12, 1989; revised manuscript received October 6, 1989, and accepted October 10.

Address for reprints: F. Lattanzi, MD, Istituto di Fisiologia Clinica del CNR, Via P. Savi 8, 56100 Pisa, Italy.

TABLE I Clinical Characteristics of the 33 Patients with Mitral Valve Disease

	Age (yrs),	Mitral		
Pt	Sex	Valve Disease	Etiology	Histology
1	44, F	MS		
2	62, M	MR	Rheumatic	FI
3	58, F	MS	Ischemic	FI
4	39. F	MS + MR	Rheumatic	FI
5	61, F	MS + MR	Rheumatic	FI
6	68, F	MR	Rheumatic	FI
7	72, M	MR	Degenerative	FI
8	48, F	MS	Degenerative	FI
9	35, F	MR	Rheumatic	FI
10	64, M	MS + MR	Rheumatic	FI
11	69. F	MR	Rheumatic	FI
12	57. F	MS	Rheumatic Rheumatic	FI FI
13	70, F	MS + MR		The Control of Life Street
14	69. F	MS	Degenerative Rheumatic	FI
15	74, M	MS + MR		CA
16	44. F	MS	Degenerative Rheumatic	CA CA
17	68, M	MS + MR	Rheumatic	CA
18	68. F	MS	Rheumatic	CA
19	75, M	MS + MR	Degenerative	CA
20	73, F	MS	Rheumatic	CA
21	49. M	MS	Rheumatic	CA
22	76, M	MR	Degenerative	CA
23	74, F	MS + MR	Degenerative	CA
24	52, F	MS	Rheumatic	CA
25	68, F	MR	Rheumatic	CA
26	69, F	MS + MR	Rheumatic	CA
27	48, F	MS	Rheumatic	CA
28	71, F	MS + MR	Degenerative	CA
29	70, M	MR	Degenerative	CA
30	67, F	MS	Rheumatic	CA
31	54, F	MS	Rheumatic	CA
32	69, F	MS + MS	Rheumatic	CA
33	48, F	MS	Rheumatic	CA
The state of the s				

CA = calcific mitral valve; degenerative = no history of acute rheumatic fever; FI = fibrotic mitral valve; ischemic = rupture (partial) of papillary muscle after myocardial infarction; MR = mitral regurgitation; MS = mitral stenosis; rheumatic every of

Echocardiographic examination: Both patients and control subjects underwent quantitative analysis with an M-mode echocardiograph connected to the acquisition system. The parasternal window was used in every patient, because this approach is the easiest to perform,

from the technical point of view, with the M-mode technique. For every subject, the mitral and pericardial reflections were considered.

Both anterior and posterior leaflets were analyzed for the mitral valve. For each structure, several measurements were performed and the maximal value was considered representative of that structure. The pericardial view was obtained behind the mitral leaflets, to avoid the exploring ultrasound beam crossing the mitral echoes, because this could generate different attenuation in pericardial echo intensity.

Ultrasonic method: A diagram of the data acquisition system is shown in Figure 1. An OTE Biomedica 2310 M-mode echocardiograph (with an A-mode screen as well) was used for guidance and to provide an electrocardiographic signal. Traditional M-mode echocardiographic technique was used for spatial localization; quantitative analysis of backscattered ultrasound was performed on the tissue in the region of interest. Details of the system have already been given elsewhere.5

A 2.25-MHz single frequency transducer (1.3 cm diameter, focal distance 7 cm, focal region 6 cm) was used. The "native" radiofrequency signal (Figure 2) was sampled before the processing chain of the M-mode instrument. Sampling is performed by a flash converter with 8 bits of amplitude resolution, at a rate of 40 MHz. The digitized signal, from an analog to digital converter, is elaborated by a microprocessor-based system. For pericardial analysis, the gate length was kept at 3 µs, which corresponds to 2.35 mm, given the velocity of ultrasound in biologic tissues of 1.57 mm/µs; for mitral valve analysis, the gate length was kept at 1 µs, which corresponds to 0.8 mm. Because mitral leaflets and pericardial surfaces generally give echoes of mostly specular type,7 the sample gate was positioned on the echo that appeared as the highest in the time domain. The acquisition of mitral valve signal was performed during diastole.

The microprocessor-based analysis involved the measure of integrated amplitude of the rectified signal. The integrated backscatter index was calculated as:  $\int |u(t)|$ 

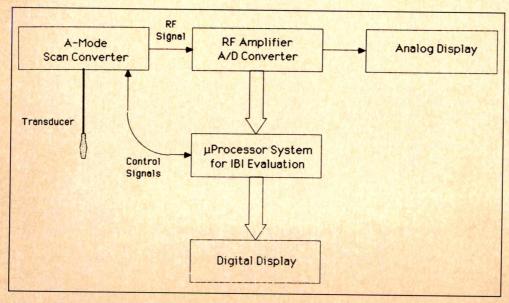


FIGURE 1. Diagram of the ultrasonic data acquisition system. IBI = integrated backscatter index; RF = radiofrequency.

dt, where  $|\cdot|$  = the absolute value;  $u(t) = i(t) \times s(t)$ ; i(t) = the time sequence of backscattered echoes; and s(t) = the time gate delimiting the thickness of the insonated tissue.

During the examination, the integrated backscatter index (expressed in mV, a linear value) was constantly visualized on a digital display, to allow the on-line measurements

The integrated backscatter index results for each mitral valve were processed off line and expressed in a percent value, assuming 100% to be the pericardial interface (from which the maximum echo intensity was consistently recorded in normal heart).<sup>5,8</sup> Echo intensity was calculated as follows: mitral valve/pericardial valve × 100. The aim of this device is to eliminate possible sources of error regarding the attenuation of reflection from patient to patient, due to the interposed tissue and to the depth of the target in the chest.

The integrated backscatter index primary values were also presented (in dB, a logarithmic unit measurement of sound). They were calculated as follows: 20 log V/V reference (where V = value of heart structure insonated; V reference = value of a reference specular reflector with very high reflection intensity; V and V reference are primary integrated backscatter index values and are expressed in mV).

Pathologic characterization: The excised mitral valves were processed for hematoxylin-eosin staining, Weigert's method for elastic fibers, Van Gieson stain for collagen and the silver method of von Kossa for the demonstration of calcium deposits was also used. Light microscopic examination of the whole valve (5 sections of each specimen) was carried out at low magnification (× 100) and the amount of scarry fibrous and calcific tissue was evaluated by 2 independent observers blinded to the ultrasonic results. The valve was considered calcific when calcium deposits were observed in >10% of microscopic fields and when at least 1 calcium deposit >2 mm was present. These arbitrary criteria were adopted to differentiate the microcalcific scarry specimens from the calcific group. Scarry fibrous tissue was observed in every excised mitral valve; therefore none of these specimens was considered normal. The decision of the 2 observers was always unanimous.

**Statistical analysis:** For each index the mean and standard deviation were measured. Differences were tested for significance by analysis of variance, with subgroup analysis by the Duncan test. Due to the large intergroup difference of standard deviation, the percent integrated backscatter index values underwent a natural logarithmic transformation before the statistical analysis.

### RESULTS

On the basis of histologic findings, the excised valves were separated into 2 groups: fibrotic (13 samples) and calcific (20 samples). None of the excised mitral valves were classified as normal, because none had completely normal tissue in any microscopic field.

Accordingly, 4 subsets of subjects were identified: group I (young control subjects), group II (older control subjects), group III (patients with fibrotic mitral valve)

and group IV (patients with calcific mitral valve). For the ultrasound analysis, the pericardium percent integrated backscatter index was, by definition, 100% in all patients. Overall, the percent integrated backscatter index of the mitral valve differed significantly in the 3 groups and only a low degree of overlap was present (Table II, Figure 3).

The overall primary integrated backscatter indexes of the structures for each group are listed in Table II. In this case, the integrated backscatter index is expressed in dB, as previously defined. There is no significant difference among the overall pericardium values of the 4 groups, but a large standard deviation is present; for mitral valves, a statistically significant difference among the young control subjects and patient groups persists, although a major degree of overlap is present (Figure 4)

For the group of older normal subjects, age-matched with patients with mitral valve disease, the values of the primary integrated backscatter index ( $66 \pm 9$ , difference not significant vs group I and p <0.01 versus groups III and IV) and percent integrated backscatter index ( $8 \pm 4$ , p <0.05 and p <0.01, respectively) are

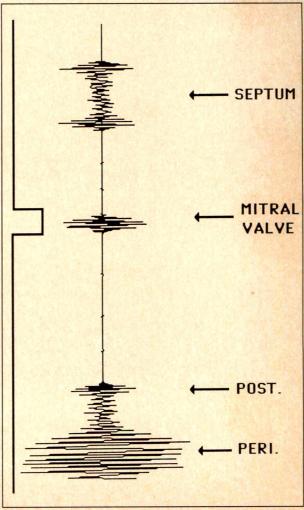


FIGURE 2. Schematic representation of a radiofrequency signal coming from a calcific mitral valve (POST = posterior wall; PERI = pericardium). The acquisition time gate is represented on the *left*.

TABLE II Values of Primary and Percent Integrated Backscatter Index in the Four Groups

a series									
Group	No.	Pericardial IBI (dB)	Mitral IBI (dB)	Mitral IBI (%)					
1	10	$-8.8 \pm 5.3$	-73.1 ± 6.9	4.6 ± 2.1					
11	10	$-9.5 \pm 4.7$	-66.6 ± 9.1	8.1 ± 3.6					
III	13	$-10.7 \pm 5.4$	-46.4 ± 13.2	17.0 ± 8.8					
IV	20	$-10.4 \pm 7.0$	$-28.0 \pm 19.1$	$52.4 \pm 29.7$					

intermediate between those of the young control group and patients with histologically assessed fibrotic mitral valve, but they are clearly closer to group I values.

#### DISCUSSION

Our data are consistent with previously reported in vitro findings. In fact, although echo reflections from the mitral leaflet are mostly of the specular type,<sup>7</sup> it is possible in vitro to differentiate normal, fibrotic and calcific excised mitral valve by means of a simple quantitative ultrasound index measuring the radiofrequency reflection intensity. In part, an increase in echo intensity occurs when fibrosis or calcification involves the mitral leaflet. This is probably due to the presence of echogenic interfaces originated by fibrotic and, especially, calcific laminae.

As mentioned, an increase in fibrotic content, due to the physiologic "aging" of tissue, is usually present in mitral leaflets of older subjects, although function and qualitative echocardiographic appearance will be normal. This condition is probably the cause of the statistically significant difference in the quantitative backscatter index between young and older subjects.

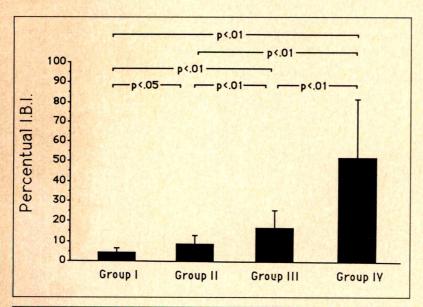


FIGURE 3. Histogram of the overall percent integrated backscatter index (IBI) value of the mitral valves of the 4 groups of subjects.

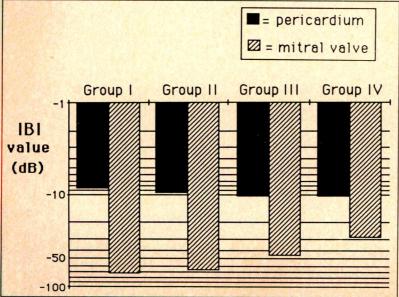


FIGURE 4. Histogram of the overall primary integrated backscatter index (IBI) value coming from the pericardium and from mitral valve of the 4 groups of subjects. The values are negative and in logarithmic scale, because they are expressed in dB, which is a reference unit (see text).

Data are mean ± standard deviation.

\* p <0.05; f p <0.01.

% = percent integrated backscatter index (IBI) value with respect to pericardial value (100% in all patients).

Limitations: There are many well-known sources of error that can affect ultrasound findings in patients and that could, at least partially, account for the low degree of overlap in the integrated backscatter index value of the 4 groups of patients.

In particular, the interrogating and reflected beam underwent an attenuation that was variable from patient to patient because of differences in chest morphology, the thickness and attenuation power of the biologic structures and the distance of the target from the transducer.

Another problem is the continuous movement of mitral leaflets during the cardiac cycle; in fact, as mitral reflections are especially of the specular type, the echo intensity is angle dependent. It is maximal when the incidence of the interrogating beam and the leaflet surface is orthogonal and decreases dramatically when the angle changes. We minimized this problem, in part, measuring the integrated backscatter index value of mitral leaflets during diastole when the leaflet is usually almost perpendicular to the ultrasound beam. Of course, differences in angles are unavoidable from patient to patient and from measurement to measurement; however, for each structure studied, the maximal value was always considered. These limitations regarding the uncertainties in structure position should be overcome by the use of an analysis system utilizing a bidimensional echocardiograph.6

Comparison with conventional echocardiographic findings: Qualitative conventional echocardiographic evaluation often provides the impression of an increase in echo intensity from mitral leaflets in patients with mitral valve disease and the valve is often qualitatively described as fibrotic or calcific. However, this information has limited diagnostic accuracy9-13 and is strongly dependent on the operator's skill as well as on the instrument characteristics, which may mask or mimic changes in the texture of ultrasound images.

The clinical and practical implications of noninvasive quantitative characterization of the mitral valve might be important. Mitral valve commisurotomy remains a good alternative to replacement in some patients with mitral stenosis. Because calcification and dense fibrosis represent a contraindication to commisurotomy, 14 it is important for the surgeon to have reliable preoperative information about valve structural involvement as well as about anatomic and functional impairment. Finally, the use of percutaneous transvenous balloon valvulotomy as a method for valve dilation in patients with mitral stenosis makes it critical to characterize the mitral valve, because the success of the procedure is strictly correlated to the pathologic involvement of the valve.15

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## **Angiographic and Electrophysiologic Substrates** of Ventricular Tachycardia in Chronic Chagasic **Myocarditis**

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Forty-three consecutive symptomatic patients with chronic Chagasic myocarditis and ventricular tachycardia (VT) underwent clinical evaluation, 24hour Holter monitoring, left ventricular angiography and electrophysiologic testing including programmed ventricular stimulation at 3 drive cycle lengths at 2 sites in the right ventricle. The mean ejection fraction was 42  $\pm$  10%. Sixteen patients had clinical sustained VT and 27 nonsustained VT. VT was reproducibly initiated in 13 of 16 (81%) patients with sustained VT and in 14 of 27 (52%) patients with nonsustained VT. Electrocardiographic conduction disturbances were seen in 15 of 16 (94%) patients with sustained VT and in 17 of 27 (63%) patients with nonsustained VT (p <0.05). Five of 16 (31%) sustained VT and none of nonsustained VT patients had left ventricular aneurysms (p <0.05). These data indicate that VT is frequently inducible in patients with sustained VT and nonsustained VT and chronic Chagasic myocarditis. An association appears to be present between conduction disturbances on the electrocardiogram, left ventricular aneurysms and development of sustained ventricular arrhythmias.

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hagas' disease is one of the most important medical problems in South America. 1-9 The most important clinical manifestation of this disease is chronic myocarditis in which cardiac dysfunction is common and there is a very high incidence of ventricular arrhythmias. 10,11 Ventricular tachycardia (VT) and left ventricular dysfunction characterize patients at high risk of sudden death in a variety of cardiac diseases. 12-21 This association is very common in Chagas' disease and in endemic areas it is the most important cause of sudden death.22 Although intracardiac electrophysiologic studies have been described in patients with sustained VT and Chagas' disease,23 no studies have been reported in patients with nonsustained VT and chronic Chagas' myocarditis. This study was undertaken to describe the clinical, angiographic and electrophysiologic characteristics of patients with VT and chronic Chagasic myocarditis.

#### **METHODS**

Forty-three consecutive patients with VT, Chagas' disease and symptoms of palpitations (30 patients) or near syncope or syncope (27 patients) were studied. VT was detected by standard electrocardiography or Holter monitoring. Patients with valvular heart disease, coronary artery disease or hypertension were excluded.

Clinically, the VT was nonsustained in 27 patients and sustained in 16. There were 24 men and 19 women, with ages ranging from 22 to 75 (mean 45  $\pm$  12) years. Twenty-two patients had a history of congestive heart failure; of these 14 were in New York Heart Association class II and 8 were in class III. Each patient was in a compensated state before enrollment in this study (Table I).

Informed consent was obtained in each patient. All antiarrhythmic drugs were discontinued for at least 5 drug half-lives before study. Clinical laboratory evaluation, 24-hour Holter monitoring, left ventricular angiography and electrophysiologic testing were performed in each patient. Patients older than 40 years also had coronary arteriography performed by either the Sones or Judkins technique in multiple views.

Electrophysiologic protocol: The electrophysiologic studies were performed with the patient in the nonsedated state under local anesthesia. Three electrode catheters were positioned in the right atrium, atrioven-

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tricular junction and right ventricle. Bipolar electrograms were recorded simultaneously with 3 surface electrocardiographic leads on a multichannel oscilloscope (Electronics for Medicine VR6) and directly on

paper.

The same stimulation protocol was used in every study. This included the introduction of 1, 2 and 3 ventricular extrastimuli during sinus rhythm and ventricular pacing at cycle lengths of 600 and 450 ms, using 1-ms rectangular pulses delivered at twice diastolic threshold. Stimulation was performed at the right ventricular apex in all patients and if arrhythmia was not induced, the stimulation protocol was repeated at the right ventricular outflow tract. This protocol has been published previously.23

Antiarrhythmic drug testing: In all patients in whom sustained VT was induced during electrophysiologic studies, programmed stimulation using the same protocol was repeated during administration of antiarrhythmic therapy.<sup>23</sup> Procainamide (20 mg/kg, no more than 1 g) (14 patients) or propafenone (2 mg/kg, no more than 140 g) (14 patients) was administered intravenously and patients were then evaluated. Mexiletine (200 mg orally every 6 hours for 3 days) and disopyramide (100 mg orally every 6 hours for 3 days) were tested in 2 patients. If efficacy was not achieved, amiodarone was evaluated after a loading dose (1 g orally for 10 days) alone or in combination with other antiarrhythmic drugs. Patients who did not achieve efficacy were discharged receiving amiodarone.

Follow-up: Patients were seen in the arrhythmia research clinic by one of the investigators 1 month after hospital discharge and every 3 months thereafter. They underwent clinical and laboratory evaluation, including 24-hour Holter monitoring, at each visit.

Definitions: Chronic Chagasic myocarditis was defined as the presence of chronic cardiomyopathy and a positive Machado Guerreiro serum complement fixation and hemaglutinin test.24

Spontaneous VT was defined as ≥3 sequential ventricular complexes at a rate of >100/min. If this arrhythmia was >30 seconds in duration or resulted in cardiovascular collapse, it was defined as sustained.

Inducible VT during the electrophysiologic study was defined as a reproducible tachycardia with ≥6 sequential ventricular complexes. If the duration was >30 seconds or cardiovascular collapse occurred, it was defined as sustained VT; if not it was considered to be nonsustained VT.

Efficacy was defined by either invasive or noninvasive techniques. In patients with sustained VT, efficacy during electrophysiologic testing was defined as prevention of initiation (≤15 complexes) in patients in whom sustained VT has been inducible at baseline. Patients in whom sustained VT was not inducible were treated only if they were severely symptomatic and efficacy, measured by Holter monitoring, equalled suppression of 100% of VT episodes and >75% reduction of the frequency of ventricular premature complexes.

Statistical analysis: The results are presented as mean ±1 standard deviation. Statistical comparisons

**TABLE I** Patient Characteristics

	No.	SuVT	NSVT
Pts	43	16	27
Sex: M/F	24/19	9/7	15/12
Symptoms			
Palpitations	30	15	15
Syncope or near syncope	27	10	17
Cardiac arrest	1	1	0
CHF			
None	21	5	16
Class II NYHA	14	7	7
Class III NYHA	8	4	4
Electrocardiographic	32	15 (94)	17 (63)*
conduction disturbances (%)			
Ejection fraction (%)	43	38%	46%
Left ventricular aneurysm (%)	5	5 (31)	0 (0)*

\* p < 0.05

CHF = congestive heart failure; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; SuVT = sustained ventricular tachycardia.

were made using the Student t test; contingency table analyses were calculated using either chi-square or Fisher's exact tests. A p value <0.05 was considered significant.

#### RESULTS

Thirty-two patients (74%) had the right bundle branch block and left anterior hemiblock pattern. Electrocardiographic conduction disturbances were more common in patients with sustained VT (15 of 16, 94%) than in patients with nonsustained VT (17 of 27, 62%) (p <0.05) (Table I).

Coronary arteriography and left ventricular angiography: Results of coronary arteriography were normal in all patients. The mean ejection fraction was 42 ± 10%. Five of 16 (31%) sustained VT patients had a left ventricular aneurysm; none of 27 nonsustained VT patients had a left ventricular aneurysm (p <0.05) (Table

Electrophysiologic studies: VT was reproducibly initiated in 27 (62%) patients. The number of extrastimuli required for VT induction was 1 in 1 patient, 2 in 15 patients and 3 in 11 patients. Sustained VT was induced in 13 of 16 (81%) patients with clinical sustained VT and 5 of 27 (18%) patients who had clinical nonsustained VT. Cardiovascular collapse requiring cardioversion during the induced VT was observed in 5 of 18 (29%) patients. Nonsustained VT was induced in 1 of 16 (6%) sustained VT patients and in 9 of 27 (33%) nonsustained VT patients.

Electrophysiologic antiarrhythmic drug testing: In the 18 patients with induced sustained VT, procainamide and propafenone were tested. Efficacy was achieved in 3 of 18 (16%) of these patients, 2 with procainamide and 1 with propafenone. One (50%) patient achieved efficacy with disopyramide. Amiodarone alone or in combination with other antiarrhythmic drugs was tested in 14 patients. Efficacy was achieved in 3 of 14 (21%) patients. In addition, an increase in the cycle length of the VT was obtained with amiodarone in 4 patients. In them, VT was also associated with more tolerable symptoms (Table II).

TABLE II Antiarrhythmic Drug Testing in Patients with Laboratory-Induced Sustained Ventricular Tachycardia Age Clin DCL /NI Follow-Up No (yrs) Arr NYHA (%) (ms) (ms) Drug (mos) Event 1 52 SuVT III 29 240 420 Am 24 CNSD 2 57 SuVT 11 23 320 NI Pp 9 CNSD 3 43 SuVT 69 410 NI Di 42 4 50 SuVT 11 40 400 NI Pc 36 5 38 SuVT 31 280 280 Am 11 6 41 SIIVT 11 46 320 430 Am 6 50 SuVT 42 440 440 Am 11 8 32 SuVT 11 53 180 NI Am-Mx 6 9 41 SuVT 50 280 400 Am 10 10 61 SuVT III 28 340 340 Am 2 Rec + CNSD 11 54 SuVT 11 35 320 320 Am 2 Rec 12 61 SuVT 11 38 320 400 Am 13 Rec 75 SuVT III 20 380 NI Am 14 44 **NSVT** 16 240 240 Am 18 15 41 NSVT 46 340 NI Am 12 16 65 **NSVT** III 43 230 230 Am 12 17 39 NSVT III 10 220 230 Am CNSD 18 **NSVT** 27 340 NI

Am = amiodarone; BCL = basal cycle length of induced SuVT; Clin Arr = clinical arrhythmia; CNSD = cardiac nonsudden death; DCL = cycle length of VT during drug therapy; Di = disopyramide; Drug/D = antiarrhythmic drug discharged from hospital; EF = ejection fraction; Mx = mexiletine; NI = VT not inducible; NYHA = New York Heart Association functional class for congestive heart failure; Pc = procainamide; Pp = propafenone; Rec = recurrence.

Electrophysiologic testing in patients with clinical nonsustained ventricular tachycardia: VT was induced in 14 of 27 (52%) patients with nonsustained VT, it was sustained in 5 of 27 (19%) and nonsustained in 9 of 27 (33%). In 13 of 27 (48%) patients, no VT was inducible.

In nonsustained VT patients, electrocardiographic conduction disturbances and heart failure were more common than in sustained VT patients. The ejection fraction was significantly lower in patients with inducible sustained VT (28 vs 50%, p <0.05).

Follow-up: The mean follow-up was 13.8 months. All patients with clinical sustained VT were discharged from the hospital receiving antiarrhythmic drugs. Nineteen of 27 (70%) nonsustained VT patients were discharged receiving antiarrhythmic drugs; 5 because of sustained VT induction and 14 because of severe symptoms. Five of 43 (12%) patients died. Death was related to worsening of congestive heart failure in all patients. The mean ejection fraction of the patients who died was 24%; only 1 had an ejection fraction >30%.

Nine patients had a recurrence of ventricular arrhythmia, 3 with sustained VT and 6 with nonsustained VT. Electrocardiographic characteristics of recurrent sustained VT were predicted by the results of electrophysiologic testing. One patient with clinical nonsustained VT and no inducible VT during electrophysiologic testing was resuscitated from an episode of ventricular fibrillation. This patient was receiving amiodarone therapy (600 mg daily), which controlled her episodes of nonsustained VT. She had an automatic defibrillator implanted after this episode.

### DISCUSSION

As in patients with ischemic heart disease, VT can occur in chronic Chagasic myocarditis. The usefulness of electrophysiologic studies in sustained VT and Chagas' disease has been suggested in a previous clinical

study.25 Our study supports this contention and extends the observation to patients with nonsustained VT.

5

Pc

Although electrophysiologic techniques are very useful in the management of patients with sustained VT, little data exist about the usefulness of these techniques in the management of patients with nonsustained VT. Sustained VT was induced in 5 of our 27 patients with clinical nonsustained VT. We considered these findings to indicate a poor prognosis and we guided the therapy of these patients with programmed stimulation. However, these findings could also be interpreted as a nonspecific response to an aggressive stimulation protocol.

Patients with clinical nonsustained VT in whom sustained VT was induced had a significantly lower ejection fraction compared to patients in whom it was not induced. Similar observations have been made in patients with coronary artery disease. 26,27

Cardiac involvement in Chagas' disease is directed at the myocardium and conduction system. Although the ejection fraction was not significantly different between patients with sustained and nonsustained VT, conduction disturbances on the surface electrocardiogram were more common in the sustained VT group. It is possible that these patients have more structural and pathologic abnormalities affecting conduction and thus facilitating spontaneous sustained reentrant arrhyth-

Clinical implications: Spontaneous and inducible sustained ventricular tachyarrhythmias in patients with Chagas' disease can be reproducibly initiated by programmed electrical stimulation in 81% of patients with sustained VT and in 52% of patients with nonsustained VT. Patients with conduction disturbances on the surface electrocardiogram, low ejection fractions and particularly those with left ventricular aneurysms are more prone to develop sustained ventricular arrhythmias and should be evaluated.

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## Regional Left Ventricular Wall Motion Abnormalities in Idiopathic Dilated Cardiomyopathy

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An evaluation and a comparison of left ventricular regional wall motion were performed in 32 patients with idiopathic dilated cardiomyopathy, none of whom had coronary artery diameter stenosis exceeding 20% in any major artery, and 17 control subjects, using frame by frame video intensity analysis of digitized ventriculograms. This technique evaluates the whole cardiac cycle in short overlapping intervals and yields information for systolic and diastolic events, without assumptions regarding the position and orientation of the ventricle. Diastolic regional wall motion abnormalities were found in 31 of 32 patients and systolic abnormalities were present in 16 patients. Asynchronous regions most commonly detected during diastole were anteroapical and apical; they were found in 19 of 32 patients. Regional contraction abnormality was observed in the apical and the anteroapical regions in 6 of 16 patients. Dilatation-induced changes in left ventricular shape exaggerate the phenomenon of higher wall stress at the apex of the normal ventricle. Basal wall motion is thus relatively preserved in dilated cardiomyopathy.

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ystolic and diastolic wall stresses are not uniform throughout the left ventricular myocardium. Thus, although cardiomyopathy is usually a global affection of the myocardium, 1,2 regional wall motion abnormalities in addition to global hypokinesis may be anticipated.3 This study exploits digital angiography to provide a more detailed picture of regional contraction and relaxation patterns in idiopathic dilated cardiomyopathy. Most earlier angiographic studies of ventricular contraction used 2-frame analysis of the left ventriculogram. Using 1 such method, Leighton et al4 found regional hypokinesia in 3 of 6 patients with cardiomyopathy of unknown type. Other investigators<sup>5,6</sup> used frame by frame analysis throughout systole to gain a more complete picture of the extent and timing of regional shortening of the left ventricle. Kreulen et al5 identified 2 groups with unclassified myocardial disease, 1 with only global hypokinesia and 1 with additional regional abnormalities. In another study the same investigators6 showed regional wall motion abnormalities in 3 patients with idiopathic dilated cardiomyopathy.

Conventional contrast ventriculographic techniques are limited by the need for a coordinate system. Internal reference systems require assumptions to correct for realignment. If these assumptions are not correct, they would render the technique less reliable. Dilatation of the ventricle obscures the location of the apex and makes corrections for realignment even less valid. This is a consideration of great importance in the study of dilated cardiomyopathy.

We have developed a video intensity technique for regional wall motion analysis that does not require geometric assumptions regarding the shape and position of the heart and is independent of a coordinate system.<sup>8,9</sup> This method uses an external reference system, and no correction is made for rotation or translation of the heart.

#### **METHODS**

Patient population: The patient population comprised 32 patients with idiopathic dilated cardiomyopathy (Table I). None had a coronary stenosis (measured diameter) exceeding 20% in any major vessel or history of myocardial infarction. The control population consisted of 17 patients, referred for evaluation of chest pain, in whom the coronary angiogram, cardiac structure and function proved normal.

Fick cardiac output was calculated, 10 except in 4 cases where thermodilution technique was used. When clinically indicated, endomyocardial biopsies were obtained from the right side of the ventricular septum.

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TABLE I Physiologic Characteristics and Mode of Left Ventriculography in the 32 Patients with Dilated Cardiomyopathy

Pt	Age (yrs), Sex	Angio	BP	ECG	EF	CI	HR	EDP	AVO <sub>2</sub>	Remarks
1	37, M	DLV	100/75	VBG	54	3.1	60	4	4.2	Hypertrophy, fibrosis
2	65, M	DLV	125/75	LA, LV	15	2.5	120	38	5.2	Hypertension, ethanol abuse
3	56, M	Levo	90/70	AF	25	2.2	84		5.7	Ethanol abuse
4	55, M	DLV	120/64		19	2.2	60	8	-	
5	30, M	Levo	110/70	SR, LV	32	2.8	75	-	-	Hypertrophy
6	53, M	DLV	120/85	LV	27	1.3	71	40	6.4	Hypertension, ethanol abuse, diabetes, sarcoidosis
-	40.14	DLV	148/100	SR	26	2.0	92	36	10.1	
7	49, M	DLV	110/70	AF	35	2.4	95	_		Fibrosis
8	63, M		156/82	LV	47	2.7	84		_	Hypertension, degenerative changes
9	57, M	Levo DLV	100/70	AF	34	2.4	81	20	5.4	法主义是 经过过多人的支票
10 11	26, M 42, M	Levo	90/65	SR	23	2.4	90		-	Ethanol abuse, hypertrophy, fibrosis
	60.14	DIV	160/100	LV	28	2.4	63	12	5.4	Hypertrophy, fibrosis
12	68, M	DLV	78/55	_	15	3.2	115	25	4.1	Eosinophilia
13	38, F	DLV	135/80	LBBB	34	2.8	126	12		Ethanol abuse
14	59, M	DLV	110/60	AF	42	2.3	50	6	4.8	Ethanol abuse
15 16	58, M 59, M	Levo DLV	98/68	AV, LA, LV	18	2.2	93	30	5.8	Ethanol abuse, hypertrophy, fibrosis
					20	2.8	63	18		Hypertension
17	58, F	Levo	162/90		36		120	_	_	Hypertension, drug abuse,
18	29, M	Levo	110/85*	AF	25					normal biopsy
19	58, M	Levo	160/75	SR, PQT	40	1.9	66	-	6.9	Ethanol abuse, hypertrophy
20	43, M	Levo	130/100	AF	26	2.0	90	26		Normal biopsy
21	75, F	DLV	150/70	AF	30	2.1	80	10	6.0	Fibrosis
22	49, M	DLV	100/60	LBBB, PQT	36	2.9	84	20	4.7	Ethanol abuse
23	61, M	DLV	130/90	AF	38	2.3	91	17	5.6	Ethanol abuse
24	32, M	DLV	90/70	SR	27	2.2	104	24	5.9	Hypertrophy
25	57, F	DLV	80/55		29	3.2	67	16	4.0	Hypertrophy
26	50, M	DLV	86/60	SR	35	2.9	84	7	5.4	
27	—, M	DLV	-/-		28	_	100	_	-	Normal biopsy
28	64, M	DLV	98/65	RBBB	24	1.6	97	27	8.3	Ethanol abuse
29	39, F	DLV	114/100	PQT	28	1.8	135	28	7.3	Ethanol abuse, normal biopsy
30	54, M	DLV	100/60	SR	24	2.0	70	3	6.0	
	70, M	DLV	100/70	LV	26	1.8	97	16	7.3	Normal biopsy
31	70, M 58, M	DLV	130/90	AF, LV	29	1.4	100	12	7.5	Ethanol abuse, degenerative change

\* cuff pressure.

AF = atrial fibrillation; AV = first-degree atrioventricular block; AVO<sub>2</sub> = arterial venous oxygen saturation difference (volume %); BP = arterial blood pressure (mm Hg); CI = cardiac index (liters/min/m²); DLV = direct ventriculogram; ECG = electrocardiogram; EDP = left ventricular end-diastolic pressure (mm Hg); EF = ejection fraction (%); HR = heart rate index (liters/min/m²); DLV = direct ventriculogram; ECG = electrocardiogram; EDP = left ventricular end-diastolic pressure (mm Hg); EF = ejection fraction (%); HR = heart rate (liters/min/m²); LA = left atrial hypertrophy; LAP = left axis deviation; LBBB = left bundle branch block; LD = both DLV and Levo; Levo = intravenous contrast injection; LV = left ventricular hypertrophy; PQT = prolonged QT interval; RBBB = right bundle branch block; SR = sinus rythm; WPW = Wolff-Parkinson-White syndrome; — = not available

Twenty-seven of the 32 patients had a long course of unexplained heart failure and were referred for cardiac catherization for definitive diagnosis, or because of worsening symptoms. The remaining 5 presented clinically with acute cardiac failure and underwent catheterization, coronary angiography and subsequent endomyocardial biopsy to exclude myocarditis and were thereafter diagnosed as dilated cardiomyopathy. Endomyocardial biopsies were performed on 18 patients.

Left ventriculography: Contrast agent was injected at 12 to 15 ml/s for 3 seconds for direct left ventriculograms, or 25 ml/s for 1.5 seconds was injected in the inferior vena cava for levophase opacification of the left ventricle. Single plane images were acquired in the 30° right anterior oblique projection. Left ventriculograms from 35 mm cine at 60 frames/s, or from video at 30 frames/s were recorded on a ¾ inch U-matic tape recorder, using a standard interlaced scanning mode. The second or third well-opacified sinus beat was analyzed. Premature ventricular beats and the succeeding 2 beats were not used. For analysis of levophase images, the best opacified sinus beat was analyzed. Levophase images were recorded under fluoroscopy using a manually

selected constant technique (70 to 75 kVP and 2 to 5 mA).

Data acquisition: The video images were digitized at a resolution of 512 × 512 × 8 bits using a Gould DeAnza video processing system, which was interfaced to a VAX 11/750 computer system. Video images acquired over 3 to 10 seconds were digitized and stored on a high speed Winchester disk drive (Figure 1), from which the beat for analysis was selected. X-ray images from film were digitized using a General Electric cine projector equipped with a video camera. Fifty consecutive frames (starting with end-diastole) were digitized.

**Preprocessing of images:** The screen was divided into 4 quadrants each  $256 \times 256$  pixels large. We displayed the original image in the upper left quadrant, time-intensity curve in the upper right and 2 processed images in the 2 lower quadrants (Figure 2). A dilated ventricle may encompass more than  $256 \times 256$  pixels. When this occurred, we used pixel averaging (9 studies) or divided the frame into 2 fields and then averaged the pixels (7 studies).

Regional wall motion technique: The detailed method has been published previously.<sup>8,9</sup> Briefly, a region of

interest is defined to include the end-diastolic and endsystolic ventricular shells. The average time-intensity curve for this region is computed for the entire cardiac cycle. For each 100 ms the intensity for a given pixel in the region of interest is correlated with the average intensity for the whole ventricle to yield values for the slope and correlation coefficient of this relation. Two functional images, slope and correlation coefficient, are created by inserting for each 100 ms intervals in each pixel location the calculated slope or correlation coefficient values. An image sequence is created for the whole cardiac cycle (Figure 3), by including 1 new frame and dropping the earliest to get the images for the next 100 ms interval.

A high correlation coefficient indicates that the slope value of the corresponding pixel is reliable. Positive slopes indicate that the intensity of that pixel changes in the same direction as that of the whole ventricle, i.e., its motion is synchronous. Negative slopes suggest the intensity of a given pixel changes in a direction opposite to that of the whole ventricle, that is, its movement is dyskinetic. Positive slopes <1, hypokinetic or asynchronous wall motion (i.e., the changes in intensity and thus the motion) are in the same direction but of lesser magnitude than that of the whole ventricle (Figure 4).

Definitions of abnormality and regions: The sequence of images is visually examined for regions in the ventricular shell with negative or positive slopes <1 that differ from the rest of the ventricular shell. These re-

gions represent contraction or relaxation abnormalities. We defined synchronous wall motion as the absence of any such region occupying >2% of the ventricular area.

The duration of abnormality was calculated as (n -1) × (frame time) + 100 ms, where n is the consecutive number of images with abnormality.

For descriptive purposes, we divided the ventricular image into 6 regions as shown in Figure 5.

Statistical analysis: The data were analyzed using the chi-square test.11 Significance was defined as p < 0.05.

#### RESULTS

Physiological parameters: CONTROL GROUP: Systolic blood pressure ranged from 90 to 140 mm Hg and diastolic from 40 to 90 mm Hg. The mean (± standard deviation) heart rate was 65 ± 12 beats/min. Mean ejection fraction was 69 ± 7%. End-diastolic pressure measured in 12 subjects ranged from 2 to 14 mm Hg.

PATIENT GROUP: Mean blood pressure was 116/75 mm Hg, heart rate 111 beats/min and ejection fraction 30%. In 30 patients cardiac output was measured, with a mean of 2.3 liters/min/m<sup>2</sup>. Arteriovenous oxygen difference was measured in 22 patients with an average value of 6.0 vol%. Average end-diastolic pressure was 19 mm Hg (Table I). S<sub>3</sub> was present in 17 patients, absent in 13 and in the remaining 2 was not mentioned.

Wall motion: CONTROL GROUP: We found slopes >1 throughout the cardiac cycle in the whole ventricular

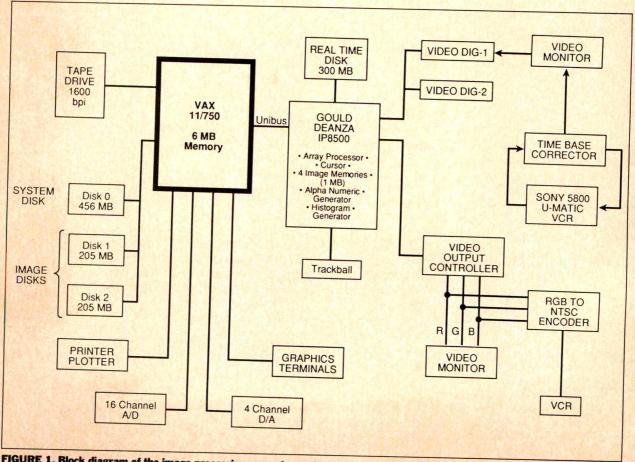


FIGURE 1. Block diagram of the image processing computer system.

shell, which defines normal wall motion for our method. Although the slopes in the apical region were >1 and thus by definition were within the normal range, these values were slightly lower than for the rest of the ventricle. This indicates that in the normal heart, wall motion in the region of the apex is less than in other regions of the left ventricle.

PATIENT GROUP: Diastolic regional wall motion abnormalities were the most common. In 31 of 32 patients early diastolic relaxation abnormalities were detected (p <0.001). In 7, additional regional asynchrony was also noted later in diastole. Forty percent of regional contraction abnormalities occurred in early systole, but in 3 patients the asynchronous contraction appeared in late systole. In 1 patient with an ejection fraction of 15%, no regional asynchrony was detected.

Localization of abnormality: The region most often involved was the anteroapical (12 patients) and the apex (11 patients). In diastole there was a clear dominance of abnormalities at the apex and the lateral wall (40 areas). Apical dominance was also seen for systolic asynchrony (Table II). In 16 patients only 1 abnormal region was detected; ≥2 abnormal regions were found in 15 patients.

**Size, duration and degree of asynchrony:** The degree of abnormality was assessed for both duration and extent. The size of the abnormal area is given as a percentage of the diastolic ventricular silhouette. The abnormal area varied from 2 to 25%. The slope images used pseudocolor to distinguish subtle changes in slope values. These changes also can be shown in black and white, albeit less clearly (Figure 6). The duration of asynchrony varied between 117 and 234 ms in the contracting phase and between 100 and 250 ms in diastole.

We calculated the mean value of the slopes for the abnormal regions, and it varied between -3.20 (high degree of asynchrony) to 0.68 (mild hypokinesia). Even when the slope value for the abnormal region was not much below 1, in all cases it was clearly different from the rest of the ventricular shell (Figure 7). The correlation coefficient image helped in identifying the subtle abnormal regions, because the correlation values were at the extremes (close to -1 or +1).

#### DISCUSSION

Diastolic abnormalities: Most previously used methods<sup>12-14</sup> evaluated only systolic wall motion. We believe that neglecting diastole underestimates the frequency of regional wall motion abnormalities, because most of the abnormalities we found occurred in early diastole. The advantage of our method is that no assumptions regarding ventricular geometry are made, and the method does not depend on an internal reference system. Furthermore, precise identification of end-systole,<sup>15</sup> a prerequisite of traditional methods, is unnecessary. Apart from the methodologic considerations, dilated ventricles are difficult to image adequately for conventional analyses by edge detection.

An explanation for regional diastolic asynchrony is the loss of myocardial elasticity in dilated ventricles. The level of cyclic adenosine monophosphate as well as calcium has been shown to differ from the normal state

TABLE II Localization of Wall Motion Abnormalities

Systole Diastole

	Systole Regions	Diastole Regions
Anterobasal	4	10
Anterolateral	3	7
Anteroapical	2	12
Apical	4	11
Inferoapical	3	4
Inferior	1	5

in patients with heart failure, 16 and may result in impaired relaxation.

Causes of regional abnormality: Previous investigators have attempted to show a relation between fibrosis and abnormal contractile patterns in patients with cardiomyopathy.<sup>3,17</sup> While asynergy is common in patients with extensive fibrosis, the absence of fibrosis does not mean wall motion will be normal. Thus, in our population, fibrosis was seen in only 6 of 18 biopsy samples, but in 17 of them regional wall motion was abnormal. We assume that biopsy of the septum was reasonably representative of the whole ventricle.

Diastolic regional asynchrony did not correlate with the presence of S<sub>3</sub> in this heterogenous population with dilated cardiomyopathy. S<sub>3</sub> is related to abnormal early rapid filling, which was not examined in this study and in any case relates more to global than regional function

Dilatation of the ventricle induces a significant change in shape, causing abnormal fiber orientation and thereby altered wall stress and compliance. 18-20 Hammermeister et al 19 showed that in the normal left ventricle, the onset of systolic motion is delayed and its extent is diminished in the anteroapical region. They attributed

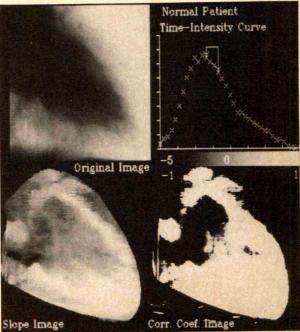
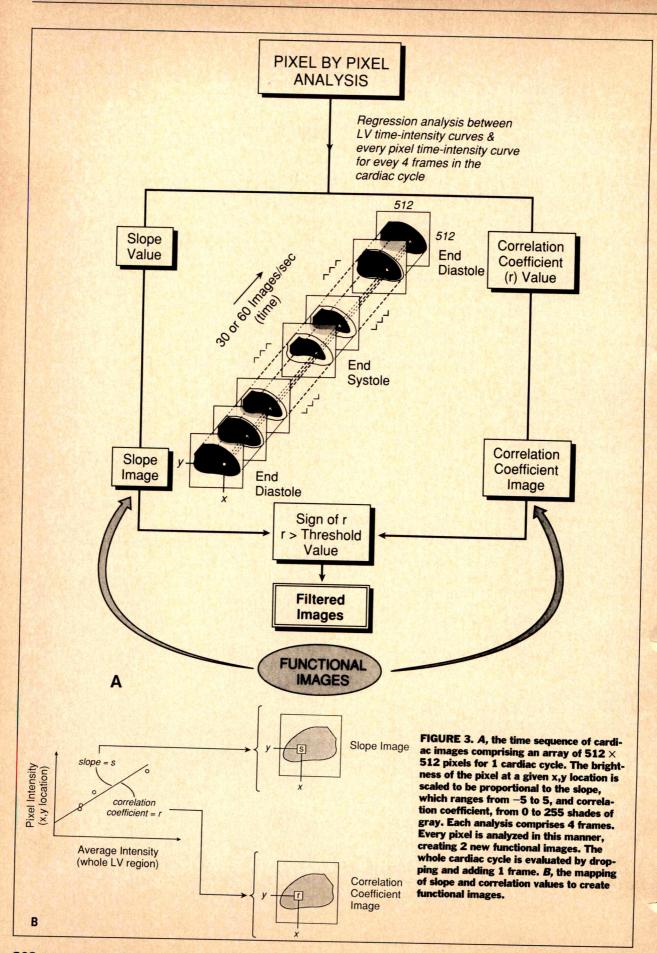


FIGURE 2. The format of the processed output for a normal subject shown in early systole indicated by 2 *vertical arrows*. Each quadrant is 256  $\times$  256 pixels.



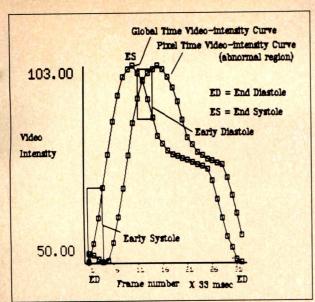


FIGURE 4. The global intensity curve and a curve for the intensity at a given pixel location are shown. Within the rectangle that encompasses early systole, the global intensity increases whereas that for a single pixel decreases yielding a negative slope. This means that the contraction at that point is opposite to that of the rest of the ventricle. Within the rectangle encompassing early diastole the same trend is noticed.

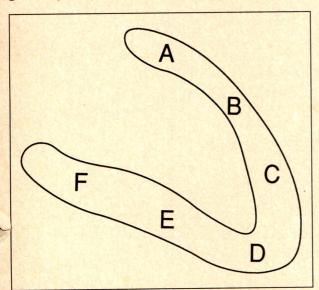


FIGURE 5. The descriptive regions. A = anterobasal; B = anterolateral; C = anteroapical; D = apical; E = inferoapical; F = inferior.

these features to late electrical activation, increased afterload secondary to contraction elsewhere in the ventricle and the lack of organized fiber orientation. This delay in activating the apex has also been shown by others. <sup>21,22</sup> In our normal population we noticed a similar trend, with the apex being relatively hypocontractile, but within the normal range and in phase with the rest of the ventricular wall in early systole. Thus, the apex is normally subject to greater wall stress and it is not surprising that it is the region most affected in heart muscle disease in both systole and early diastole. In the normal setting the radius of curvature at the apex is small compared to the rest of the ventricle leading to lower

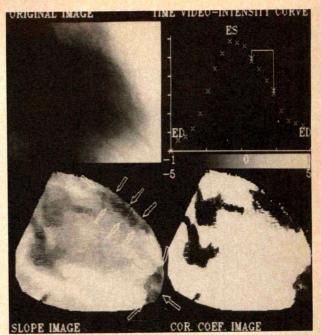


FIGURE 6. The *arrows* point to the abnormal area, appearing dark compared to the surrounding white shell, representing normal functioning ventricle. ED = end-diastole; ES = end-systole.

wall stress.<sup>23</sup> With dilatation the ventricle becomes more spherical and the apex loses its protective small radius of curvature. Another consequence of left ventricular dilatation is that the apical myocardium, which normally is the thinnest, becomes further reduced in thickness, and thereby wall stress is increased, resulting in delayed contraction and relaxation in this region.

Even in the normal ventricle wall stress is high in the vicinity of the cardiac apex. When the ventricle dilates, a number of factors combine to further elevate ventricular systolic and diastolic stress at the apex. We suggest that this may be the reason why in most patients with dilated cardiomyopathy, systolic and diastolic function is better preserved at the base of the left ventricle than at the apex.

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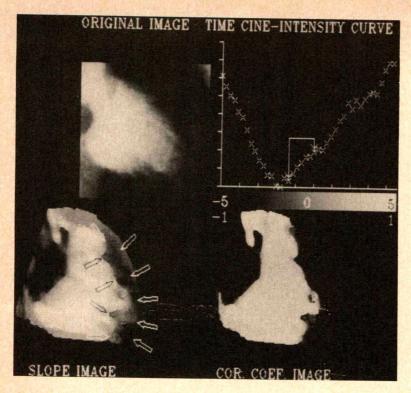


FIGURE 7. Left ventriculogram of a patient with cardiomyopathy and relaxation asynchrony at early diastole.

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## Association of Echocardiographic Left Ventricular Mass with Body Size, Blood Pressure and Physical Activity (The Framingham Study)

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Left ventricular (LV) hypertrophy has been found to predispose to increased cardiovascular morbidity and mortality. To assess the clinical correlates and potential determinants of LV mass, the relation of echocardiographically determined LV mass to a variety of clinical parameters was examined in a general population. From 1979 to 1983 Framingham Heart Study participants underwent routine evaluation including medical history, physical examination and M-mode echocardiography. LV mass was determined using an anatomically validated formula that incorporates measurements of LV wall thickness and LV internal diameter. The study population consisted of 2,226 men and 2,746 women (mean age 51 years, range 17 to 90). Age, height, systolic blood pressure and body mass index (a measure of obesity) were statistically significant and independent correlates of LV mass in both sexes (p <0.001). In men under age 50, leisuretime physical activity was associated with LV mass (p <0.05), but this was not observed in women. Results from multivariate analyses in which body mass index and subscapular skinfold thickness were included suggest that lean body mass is correlated with LV mass. Maintenance of ideal body weight and normal blood pressure, weight reduction in obese persons and blood pressure control in hypertensive patients may contribute to the primary and secondary prevention of LV hypertrophy and its sequelae. Clinical interpretation of echocardiograms should include consideration of the correlates of LV mass to gain better insight into the pathogenesis of LV hypertrophy.

(Am J Cardiol 1990;65:371-376)

orrelates and potential determinants of echocardiographically assessed left ventricular (LV) mass have been described in selected populations. Attention has focused on age, measures of body size, blood pressure and physical activity level as important potential determinants of echocardiographic LV mass in the general population.1-9 Emerging data suggest that echocardiographically detected LV hypertrophy, like its electrocardiographic counterpart, is associated with increased risk for cardiovascular disease sequelae. 10,11 Efforts to obtain a better understanding of the determinants of LV mass may aid in strategies directed toward the primary and secondary prevention of LV hypertrophy and its consequences. Routine examination of the Framingham Study sample has allowed the multivariate assessment of a variety of clinical variables as potential determinants of LV mass.

#### **METHODS**

Study design and selection criteria for the original Framingham population-based sample and their offspring (and spouses of the offspring) have been described previously. <sup>12-15</sup> Clinical examinations included measurement of height, weight, blood pressure and subscapular skinfold.

From 1979 to 1983, M-mode echocardiograms were performed on 2,291 surviving original cohort participants undergoing their sixteenth biennial examination and 3,857 offspring undergoing their second examination. Echocardiograms of adequate quality to assess LV mass were obtained in 1,365 (60%) of the original cohort participants (mean age 69 years, range 59 to 90) and 3,607 (94%) of the Offspring Study participants (mean age 44 years, range 17 to 75). As previously reported, participants with inadequate echocardiograms were more likely to be older, to have a lower vital capacity and to have overt cardiovascular disease compared to those with adequate studies. <sup>16</sup>

Leisure-time physical activity was assessed by questionnaire in the Offspring Study only.<sup>17</sup> Participants were asked to recall their leisure activities using a list of activities as a reminder. The participants also gave the average time per week engaged in each activity as well as the number of weeks during the previous year of participation in that activity. Using energy equivalents derived from review of published values,<sup>17</sup> kilocalories expended in leisure activity each week (averaged over the previous year) were estimated. To assess the effects of conditioning, participants were classified based on

From the Framingham Heart Study, National Heart, Lung, and Blood Institute, Framingham, Massachusetts, and the Epidemiology and Biometry Program, National Heart, Lung, and Blood Institute, Bethesda, Maryland. Manuscript received July 27, 1989; revised manuscript received September 25, 1989, and accepted September 26.

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TABLE I Characteristics of Participants with Adequate Echocardiograms in the Framingham Study Ages 18 to 90 Years (Cohort Examination 16 and Offspring Cycle 2, 1979 to

Observats vistin	Men	Women
Characteristic	(n = 2,226)	(n = 2,746)
Age (yrs)	50 ± 14	52 ± 15
Weight (kg)	81 ± 12	$64 \pm 12$
Height (cm)	175 ± 8	160 ± 7
Body surface area (m <sup>2</sup> )	2.0 ± .2	$1.7 \pm .2$
Body mass index (kg/m²)	27 ± 4	25 ± 5
Subscapular skinfold (mm)	21 ± 9	$21 \pm 10$
Systolic pressure (mm Hg)	$129 \pm 18$	$125 \pm 21$
Diastolic pressure (mm Hg)	81 ± 10	$76 \pm 10$
LV mass (Penn) (g)	$202 \pm 62$	$136 \pm 44$
LV mass/BSA (g/m²)	$103 \pm 30$	82 ± 25
LV mass/height (g/m)	116 ± 35	$85 \pm 28$

whether or not they reported spending at least 1 hour/ week averaged over the past year in conditioning activities (defined as those expending at least 7.5 kilocalories/min).17

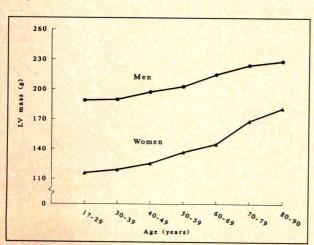


FIGURE 1. Mean left ventricular mass by sex and by age among participants aged 17 to 90 years. Framingham Study, cohort examination 16 and offspring cycle 2, 1979 to 1983.

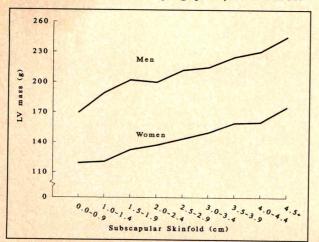


FIGURE 2. Mean left ventricular mass by sex and by subscapular skinfold among participants aged 17 to 90 years. Framingham Study, cohort examination 16 and offspring cycle 2, 1979 to 1983.

TABLE II Age-Adjusted Increments for Left Ventricular Mass (in g) for Independent Variables in Framingham Study Participants Ages 17 to 90 Years (Cohort Examination 16 and Offspring Cycle 2, 1979 to 1983)

Independent Variable:	Men	Women
Difference	(n = 2,226)	(n = 2,746)
Weight: 10 kg	21*	16*
Height: 10 cm	17*	11*
Body mass index: 2 kg/m <sup>2</sup>	12*	8*
Body surface area: 0.1 m <sup>2</sup>	15*	12*
Subscapular skinfold: 10 mm	13*	12*
Systolic pressure: 20 mm Hg	12*	8*
Diastolic pressure: 10 mm Hg	6*	4*

p < 0.001 Values are left ventricular mass estimates for the unit increments of the independent variables.

Participants were studied using a standard M-mode echocardiographic technique as previously described.1 Measurements were made according to the Penn convention described by Devereux and Reichek<sup>18</sup>: LV mass (g) =  $1.04 [(LVID + VST + PWT)^3 - (LVID)^3] -$ 13.6; where LVID = diastolic LV internal diameter; VST = diastolic ventricular septal thickness, and PWT = diastolic posterior wall thickness.

Simple least-squares linear regression techniques were used to estimate and test the significance of the relation between LV mass and age, blood pressure, physical activity and various measures of body habitus. Sex-specific mean LV mass was calculated by levels of age, subscapular skinfold, systolic blood pressure and weekly physical activity expenditure in separate analyses. Sex-specific mean LV mass was also calculated by tertiles of body mass index and systolic blood pressure jointly. Stepwise multiple regression analysis (Statistical Analysis Systems) was used to assess the joint effects of

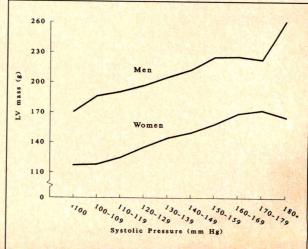


FIGURE 3. Mean left ventricular mass by sex and by systolic pressure, including participants taking antihypertensive medications, aged 17 to 90 years. Framingham Study, cohort examination 16 and offspring cycle 2, 1979 to 1983.

various attributes as potential determinants of echocardiographic LV mass.

#### RESULTS

The characteristics of the 4,972 participants in the total study group with adequate echocardiograms are listed in Table I. For men and women, respectively, mean values are 50 and 52 years of age, 81 and 64 kg of weight, 175 and 160 cm of height, 27 and 25 kg/m<sup>2</sup> of body mass and 202 and 136 g of LV mass.

Linear regression coefficients were used to estimate age-adjusted increments of LV mass (in grams) for specific differences in levels of selected independent variables known to correlate with LV mass (Table II). The unadjusted LV mass increments/10 years of age were 8.2 g in men (p <0.001) and 11.1 g in women (p <0.001). After age-adjustment, weight, height, body mass index, body surface area, subscapular skinfold and systolic and diastolic blood pressures were all significantly related to LV mass (p <0.001) in both men and women.

LV mass increases with age, subscapular skinfold and systolic blood pressure in both men and women. Mean LV mass in participants aged 17 to 29 years compared to 80 to 90 years increased from 189 to 228 g in men and from 116 to 181 g in women (Figure 1). For subscapular skinfolds from <1.0 cm to ≥4.5 cm mean LV mass increased from 170 to 245 g for men and from 119 to 175 g for women (Figure 2). In participants with a systolic pressure of <100 mm Hg compared to ≥180 mm Hg, mean LV mass increased from 171 to 260 g in men and from 117 to 165 g in women (Figure 3). An analysis that excluded participants taking antihypertensive medication showed similar results.

Compared to age, skinfold and blood pressure, the association between level of physical activity and LV mass is less consistent in this relatively sedentary population. Among participants aged 50 years or older, only 15 of 559 (2.7%) men and 7 of 557 women (1.3%) par-

TABLE III Age-Specific Means and Multivariate Regression Analysis of Left Ventricular Mass in Relation to Physical Activity in Framingham Offspring Men (Cycle 2, 1979 to 1983)

Age (yrs)	18 to 29	30 to 39	40 to 49	50+
No.	117	418	511	559
Mean kcal per week	1,473	1,502	1,371	1,278
Percent participating in	24	22	10	3
conditioning activities*				
Increment <sup>†</sup> in LV mass (g)	4.6	2.5	2.5	-0.9
1,000 kcal/week	p = 0.018	p = 0.055	p = 0.044	p = 0.489
averaged over year				-
Increment <sup>†</sup> in LV mass (g):	22.0	5.1	12.8	-6.1
for participation	p = 0.010	p = 0.311	p = 0.052	p=0.613
in conditioning				
(yes/no) activities*				
				and the state of t

<sup>\*</sup> Participation in conditioning activities = at least 1 hour/week averaged over the previous year of activity requiring 7.5 kcal/min.

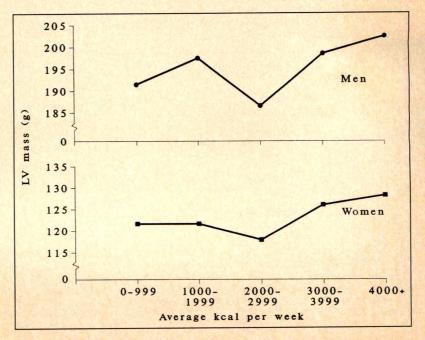
1 Adjusted for height, body mass index, subscapular skinfold and systolic blood pressure.

ticipated in at least 1 hour of conditioning activities (≥7.5 kcal/min) per week averaged over the year (Table III).

Age-specific multivariate regression coefficients for total kilocalories per week expended in leisure-time physical activities in relation to LV mass were positive and significant only for men aged 18 to 29 years (p <0.05) and age 40 to 49 years (p <0.05) (Table III). Also, the regression coefficients in Table III yield estimated increments of 5 to 22 g of LV mass/1,000 kcal of conditioning activities for men under 50 years old. In participants under age 50 expending an average of <1,000 kilocalories/week (Figure 4) compared to those expending ≥4,000 kilocalories, mean LV mass increased from 192 to 203 g in men (p = 0.024) and from 122 to 128 g in women (difference not significant).

Because systolic blood pressure and body mass index are strongly associated with echocardiographic LV mass, sex-specific mean LV mass was calculated for

FIGURE 4. Mean left ventricular mass for men and women by level of average weekly leisure-time physical activity among participants aged 17 to 49 years. Framingham Offspring Study, cycle 2, 1979 to 1983.



**TABLE IV** Multivariate Regression Analysis for Left Ventricular Mass (in g) for Independent Variables in Framingham Study Participants Ages 17 to 90 Years (Cohort Examination 16 and Offspring Cycle 2, 1979 to 1983)

Variable: Difference	Men	Women	Men	Women	Men	Women
Age: 10 years	9	9	8	10	9	9
Height: 10 cm	20	14	17	11	22	14
Systolic pressure: 20 mm Hg	8	4	11	5	8	6
Body mass index: 2 kg/m <sup>2</sup>	12	8	X	X	16	9
Subscapular skinfold: 10 mm	X	Х	11	12	-12	-5
Intercept	-402	-251	-225	-154	-456	-269

All coefficients significant at p <0.001. There were 2,226 men and 2,746 women. X = excluded in this model

joint categories of these variables. As presented for men in Figure 5 and for women in Figure 6, mean LV mass increases consistently across increasing tertiles of systolic pressure and body mass index both separately and jointly.

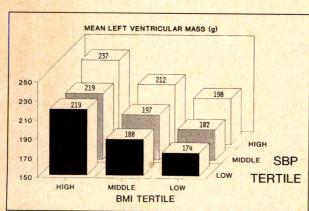


FIGURE 5. Mean left ventricular mass by tertiles of systolic pressure and body mass index for men aged 17 to 90 years. Includes participants taking antihypertensive medications. Framingham Study, cohort examination 16 and offspring cycle 2, 1979 to 1983.

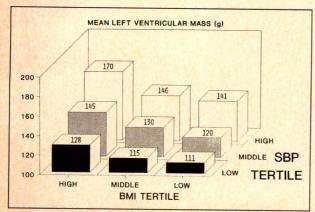


FIGURE 6. Mean left ventricular mass by tertiles of systolic pressure and body mass index for women aged 17 to 90 years, including participants taking antihypertensive medications. Framingham Study, cohort examination 16 and offspring cycle 2, 1979 to 1983.

Multivariate sex-specific regression coefficients were estimated for various models as listed in Table IV. Using the regression equations, LV mass in grams was estimated for specific increments of selected independent variables (Table IV). While all models included age, height and systolic pressure, separate models were calculated to include either body mass index or subscapular skinfold separately and together. In all models, the regression coefficients per unit change for age, height, systolic pressure, body mass index (excluding skinfold) and skinfold (excluding body mass index) in both sexes were all positively and significantly related to LV mass (p <0.001). However in the multivariate models that included both body mass index and subscapular skinfold, the coefficients for body mass index were significantly positive while those for skinfold became significantly negative (p <0.001) (Table IV).

#### DISCUSSION

The present study demonstrates significant associations between a variety of clinical parameters with echocardiographic LV mass. It includes cross-sectional measurements on both Framingham Cohort and Offspring participants. The selection biases in this large population-based sample are relatively few. Most previous studies have examined correlates of echocardiographic LV mass primarily in clinic-based series or in persons with established cardiovascular disease risk factors. 5,6,8,9,19

The increase in LV mass with age is consistent with other studies<sup>20,21</sup> and may be due to several factors. The prevalence of many of the other risk factors for increased LV mass such as elevated blood pressure, obesity, valvular disease and occult coronary artery disease tend to increase with age. While the statistically significant regression coefficient for age in the multivariate analyses suggests that increased LV mass may be a characteristic of aging cardiac muscle, it seems unclear whether increased LV mass is an inevitable consequence of aging. More detailed analyses of the relation of age to LV mass were undertaken in a healthy sample of study participants.<sup>22</sup> The conclusion was that LV mass does not increase with age and that increased LV mass is not an inevitable consequence of aging.<sup>22</sup>

The shapes of the curves relating age to LV mass differ for men and women with the decreased slope observed in men at older ages. This observation is similar to previous findings<sup>23,24</sup> and may relate to selective mortality, which is promoted in part by LV hypertrophy. In women, the accelerated slope of the curve at the time of menopause suggests the possibility of direct or indirect hormonal influence on cardiac muscle mass.

Consistent with previous reports, 4,9,25 a strong association between LV mass and blood pressure level was evident in this study. A simple physiologic explanation is that the myocardium hypertrophies in response to increased afterload. Several studies<sup>1,26,27</sup> on small samples have documented regression of LV mass as a consequence of blood pressure control. MacMahon et al7 suggest that weight loss has more of an impact on LV mass than does blood pressure control.

The association we noted between LV mass and body size is consistent with prior reports<sup>3,5,6,19</sup> and was evident for all measures examined including height, weight, body mass index, body surface area and subscapular skinfold. A likely physiologic explanation for the association of obesity with LV mass may relate to the volume demand of adipose tissue, pressure loading conditions observed in obesity or hormonal/humoral mechanisms.

The negative coefficient observed for subscapular skinfold in multivariate analyses when body mass index and skinfold were included together suggests that lean body mass (all nonadiopse tissue) is an important determinant of LV mass.

While the physical attributes identified in this report are associated with increased levels of LV mass, their pathophysiologic mechanisms of hypertrophy differ. While increased blood pressure tends to promote concentric LV hypertrophy, obesity results in LV dilation and an eccentric form of hypertrophy. It is not clear whether increased LV mass due to different mechanisms will impart the same risk for adverse sequelae.

A weak association of physical activity with LV mass was observed in men under age 50 but not in older men and not in women. The magnitude of the observed effect of physical activity (Figure 4) was small compared with subscapular skinfold (Figure 2) and systolic pressure (Figure 3). At levels of leisure-time physical activity encountered in this largely sedentary sample, it is unlikely that physical activity could produce increases in LV mass sufficient to result in LV hypertrophy.

Several limitations must be considered. Our study population was limited to subjects with adequate echocardiograms; thus there was a selection bias in favor of healthier participants. 16 Secondly, while cross-sectional data are useful to identify characteristics associated with increased LV mass, they can only suggest which attributes are the determinants of LV mass. The impact of physical activity on LV mass may be underestimated in this report because occupational activity is not included in the leisure-time physical activity questionnaire used.17 In addition, because this study population is overwhelmingly white, results are not necessarily generalizable to nonwhite groups. Further, variations in LV mass may be in part explained by factors not addressed in these analyses such as genetic, neurohumoral and endocrine factors,<sup>28</sup> blood viscosity<sup>29</sup> and alcohol intake.<sup>30</sup> Lastly, the relation of casual office blood pressure measurement may underestimate the association of blood pressure with LV mass.

The identification of a variety of potential determinants of LV mass has important diagnostic, therapeutic and preventive implications. In the interpretation of an echocardiogram, consideration of the clinical contributors to increased LV mass is necessary. For example, increased LV mass in an obese hypertensive adult may be attributed to known and modifiable factors. A similar LV mass in an adult without such risk factors needs further investigation.

The relation between echocardiographic LV mass and coronary artery disease incidence in the general

population was established in a report based on 4-year follow-up of participants in the original Framingham cohort. <sup>10</sup> A better understanding of the factors influencing the development of increased LV mass may lead to new strategies to prevent or treat LV hypertrophy. Maintenance of ideal body weight and normal blood pressure may contribute to the primary prevention of LV hypertrophy. Weight reduction in obese persons and blood pressure control among hypertensive persons may reduce the cardiovascular disease sequelae associated with LV hypertrophy through its secondary prevention or regression. <sup>7</sup> Such insights form the basis for additional experimental studies.

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INDICATIONS AND USAGE: EMINASE,\* ANISTREPLASE, is indicated for use in the management of acute myocardial infarction (AMI) in adults, for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms.

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding. EMINASE\* is contraindicated in the following situations: a citive internal bleeding history of cerebrovascular accident cecent (within 2 months) intracranial or intraspinal surgery or trauma (see WARNINGS) intracranial neoplasm, arteriovenous malformation, or aneurysm known bleeding diathesis severe, uncontrolled hypertension. EMINASE\* should not be administered to patients having experienced severe allergic reactions to either this product or Streptokinase.

■ severe, uncontrolled hypertension. EMINASE\* should not be administered to patients having experienced severe allergic reactions to either this product or Streptokinase.

WARNINGS: Bleeding: (See ADVERSE REACTIONS) The most common complication associated with EMINASE\* therapy is bleeding. The types of bleeding associated with thrombolytic therapy can be divided into two broad categories: 1. Internal bleeding involving the gastrointestinal tract, genitourinary tract, retropertioneal, ocular, or intracranial sites. 2. Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., venous cutdowns, arterial punctures, stees of recent surgical intervention). The concomitant use of heparin anticoagulation may contribute to the bleeding. Some of the hemorrhagic episodes occurred one or more days after the effects of EMINASE\* had dissipated, but while insertion sites, arterial and venous puncture sites, cutdown sites, and needle puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites, and needle puncture sites). Intramuscular injections and nonessential handling of the patient should be avoided during treatment with EMINASE\*. Venipunctures should be patient should be applied, and the puncture sites should be checked frequently for evidence of bleeding. Each patient being considered for therapy with EMINASE\* should be carefully evaluated and anticipated benefits should be excelled used and anticipated benefits should be carefully evaluated and anticipated benefits should b

Arrhythmias: Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when injections of EMINASE\* are administered.

Hypotension, sometimes severe, not secondary to bleeding or anaphylaxis, has occasionally been observed soon after intravenous EMINASE® administration. Patients should be monitored closely and, should symptomatic or alarming hypotension occur, appropriate symptomatic treatment should be administered.

PRECAUTIONS: General: Standard management of myocardial infarction should be implemented concomitantly with EMINASE\* treatment. Invasive procedures should be minimized [see WARNINGS]. Anaphylactoid reactions have rarely been reported in patients who received EMINASE\*. Accordingly, adequate treatment provisions such as epinephrine should be available for immediate use.



Readministration: Because of the increased likelihood of resistance due to antistreptokinase antibody, EMINASE® may not be as effective if administered more than 5 days after prior EMINASE® or Streptokinase therapy or streptocons.

may not be as effective if administered more than 5 days after prior EMINASE\* or Streptokinase therapy or streptococcal infection, particularly between 5 days and 6 months. Increased antistreptokinase antibody levels between 5 days and 6 months after EMINASE\* or Streptokinase administration may also increase the risk of allergic reactions. Repeated administration of EMINASE\* within one week of the initial dose has occurred in a small number of patients treated for AMI and non-AMI conditions. The incidence of hematomas/bruising was somewhat greater in those patients who received one dose.

Laboratory Tests: Intravenous administration of EMINASE\* will cause marked decreases in plasminogen and fibrinogen and increases in thrombin time (TT), activated partial thromboplastin time (APTT), and prothormbin time (PT). Results of coagulation tests and/or measures of fibrinolytic activity performed during EMINASE\* therapy may be unreliable unless specific precautions are taken to prevent in vitro artifacts. EMINASE\*, when present in blood in pharmacologic concentrations, remains active under in vitro conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (2000 to 3000 KII/mL) can, to some extent, mitigate this phenomenon.

Drug Interactions: The interaction of EMINASE\* with other cardinactive drugs has not been studied in addition to bleeding.

**Drug Interactions:** The interaction of EMINASE\* with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as aspirin and dipyridamole) may increase the risk of bleeding if administered prior to EMINASE\* therapy.

Use of Anticoagulants: EMINASE\* alone or in combination with antiplatelet agents and anticoagulants may cause bleeding complications. Therefore, careful monitoring is advised, especially at arterial puncture sites. In clinical studies, a majority of patients treated received anticoagulant therapy postdosing with EMINASE\* during their hospital stay and a minority received heparin pretreatment with EMINASE\*. The use of antiplatelet agents increased the incidence of bleeding events similarly in patients treated with EMINASE\* or nonthrombolytic therapy. There was no evidence of a synergistic effect of combined EMINASE\* and striplatelet agents no bleeding events. In addition, there was no difference in the incidence of hemorrhagic CVA's in EMINASE\* treated patients who did or did not receive aspirin.

Carcinogenesis. Mutagenesis. Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Studies to determine mutagenicity and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested.

Prepancy [Category C]: Animal reproduction studies have not been conducted with EMINASE\*. It is also not known whether EMINASE\* can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. EMINASE\* should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether EMINASE\* is excreted in human milk. Because many drugs are excreted in human milk, the physician should decide whether the patient should discontinue nursing or not receive EMINASE\*.

Pediatric Use: Safety and effectiveness of EMINASE\* in children have not been established.

ADVERSE REACTIONS: Bleeding: The incidence of bleeding (major or minor) varied widely from study to study and may depend on the use of arterial catheterization and other invasive procedures, patient population, and/or concomitant therapy. The overall incidence of bleeding in patients treated with EMINASE\* in clinical trials (in=5275) was 14.6% with nonpuncture-site bleeding occurring in 10.2%, and puncture-site bleeding occurring in 5.7%, of these patients. Bleeding intracranial bleeding within 7 days postdosing with EMINASE\* ws 0.57% (in=5275; 0.34% etiology confirmed hemorrhagic; 0.23% etiology not confirmed) compared to 0.16% (in=1249) after nonthrombolytic therapy. In the AIMS trial the overall incidence of specific bleeding events was:

Type of Bleeding	(n=500)	(n=501)	Type of Bleeding	EMINASE® (n=500)	Placebo (n=501)	Type of Bleeding	EMINASE® (n=500)	Placebo (n=501)
Puncture site Nonpuncture site hematoma Hematuria/Genitourinary Hemoptysis	4.6% 2.8% 2.4% 2.2%	<1% <1% <1% <1%	Gastrointestinal hemorrhage Intracranial Gum/Mouth Hemorrhage Epistaxis	2.0% 1.0% 1.0% <1%	1.4% <1% 0 <1%	Anemia Eye Hemorrhage Hemorrhage (unspecified)	<1% <1% <1%	<1% <1% 0

In this study there was no difference between EMINASE\* and placebo in the incidence of major bleeding events. Should serious bleeding (not controlled by local pressure) occur in a critical location (intracranial, gastrointestin retroperitoneal, pericardial), any concomitant heparin should be terminated immediately and the administration of protamine to reverse heparinization should be considered. If necessary, the bleeding tendency can be reversed will appropriate replacement therapy. Minor bleeding can be anticipated mainly at invaded or disturbed sites. If such bleeding occurs, local measures should be taken to control the bleeding (see WARNINGS).

Cardiovascular: The most frequently reported adverse experiences in EMINASE\* clinical trials (n=5275) were arrhythmia/conduction disorders which were reported in 38% control patients. Hypotension occurred in 10.4% of patients treated with EMINASE\* compared to 7.9% for patients who received nonthrombolytic treatment (see WARNINGS). in 38% of patients treated with EMINASE\* and 46% of nonthrombolytic

Allergic-type Reactions: Anaphylactic and anaphylactic and anaphylactic and anaphylactic shock in one study). These included symptoms such as bronchospasm or angioedema. Other milder or delayed effects such as urticaria, liching, flushing, rashes, and eosinophilia have been occasionally observed. A delayed purpuric rash appearing one to two weeks after treatment has been reported in 0.3% of patients. The rash may also be associated with arthralgia, ankle edema, gastrointestinal symptoms, mild hematuria, and mild proteinuria. This syndrome was self-limiting and without

Risk of Viral Transmission: Six batches of EMINASE\* (five different batches of Lys-Plasminogen) were used in clinical trials designed specifically to monitor possible hepatitis non-A, non-B transmission. No case of hepatitis was diagnosed in patients receiving EMINASE\*. Lys-Plasminogen is derived from human plasma obtained from FDA approved sources and tested for absence of viral contamination, including human immunodeficiency virus type -1 (HIV-1) and hepatitis B surface antigen, The manufacturing process includes a vapor-heat treatment step for inactivation of viruses. The entire manufacturing process has also been validated to yield a cumulative reduction of  $\geq$ 10° fold HIV-1 infectious particles, i.e.,  $\geq$ 10° infectious particles removed by vapor-heat treatment and a cumulative tool of  $\geq$ 10° fold HIV-1 infectious particles.

Casaal Relationship Unknown: Since the following experiences may also be associated with AMI or other therapy, the causal relationship to EMINASE\* administration is unknown. The following adverse experiences were infrequently (<10%) reported in clinical trials: Body as a Whole—chills, fever, headache, shock; Cardiovascular—cardiac rupture, chest pain, emboli; Dermatology—purpura, sweating; Bastraintestinal—nausea and/or vomiting; Hemic and Lymphatic—throm-bocytopenia; Metabolic and Nutritional—elevated transaminase levels; Musculoskeletal—arthralgia; Nervous—agitation, dizziness, paresthesia, tremor, vertigo; Respiratory—dyspnea, lung edema.

DOSAGE AND ADMINISTRATION: Administer EMINASE\* as soon as possible after the onset of symptoms. The recommended dose is 30 units of EMINASE\* administered only by intravenous injection over 2 to 5 minutes into an intravenous line or vein.

Reconstitution: 1. Slowly add 5 mL of Sterile Water for Injection, U.S.P., by directing the stream of fluid against the side of the vial. 2. Gently roll the vial, mixing the dry powder and fluid. Do not shake. The reconstituted preparation is a colories to pale yellow transparent solution. Before administration, the product should be visually inspected for particulate matter and discoloration. 4. Withdraw the entire contents of EMINASE\* is not administrated within 30 minutes of reconstitution, it should be discarded.

HOW SUPPLIED: EMINASE® is supplied as a sterile, lyophilized powder in 30-unit vials. NDC 57294-030-20.

Storage: Store lyophilized EMINASE® between 2-8°C (36-46°F). Do not use beyond the expiration date printed on the vial

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In acute MI, saving time is critical

Introducing new thrombolytic therapy that saves time in administration

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## In acute MI NEW ETAINASE ANISTREPLASE 30 U

## Saves lives When used within 6 hours of onset in acute MI.





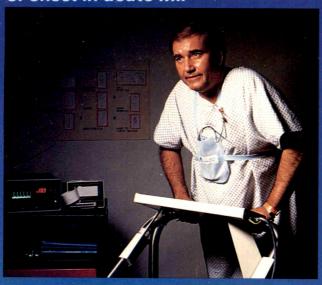
■ Documented increase in both 30-day and 1-year survival following acute MI

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# Now, a single 2- to 5-minute IV injection significantly reduces mortality in acute MI

## **Saves function**

When used within 6 hours of onset in acute MI.



- Reduces infarct size 24% compared with heparin
- Maintains significantly better ejection fraction— 53% v 47.5% with heparin

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## Saves time In administration



- Rapid administration of therapy under a physician's care
- Total 30-unit dose can be completely administered in 2 to 5 minutes

NEW EMINASE ®
ANISTREPLASE 30 U

Saves time in administration.

# EMASE 300

## Saves lives

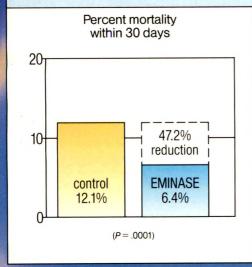
When used within 6 hours of onset in acute MI.

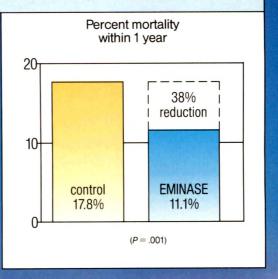
## Increases both 30-day and 1-year survival following acute MI

Eminase has been studied worldwide in more than 5200 patients and reported in the literature as APSAC (anisoylated plasminogen streptokinase activator complex).

In one multinational clinical trial involving 1258 patients with acute myocardial infarction, Eminase was significantly more effective in reducing mortality when compared with nonthrombolytic therapy. Eminase demonstrated a 47.2% reduction in mortality at 30 days and a 38% reduction at 1 year in acute MI when administered within 6 hours of onset of symptoms.\*

## Results of APSAC Intervention Mortality Study (AIMS)





\* See full prescribing information.

## **Saves function**

When used within 6 hours of onset in acute MI.

## Reduces infarct size 24%

In a double-blind randomized trial, the infarct size of Eminase patients was 24% smaller than that of heparin patients approximately 3 weeks after treatment (n = 188, P = .02).\*\*

## Improves ejection fraction

Patients treated with Eminase had significantly better left ventricular ejection fractions compared with heparin patients (53% v 47.5%; P < .01), when measured 4 days after treatment.\*\*

## Successful reperfusion

Treatment in acute MI must not only open coronary arteries, but also keep them open. Two studies report successful reperfusion with Eminase of 60%\* and 64%† Experience from these studies indicates a reocclusion rate within 24 hours of 3% to 4%.\*\*

## Presents a low incidence of serious adverse effects

Few episodes of major bleeding.

In all clinical trials (n = 5275), the incidence of intracranial bleeding was 0.57%, compared to 0.16% with nonthrombolytic therapy. The overall incidence of bleeding was 14.6% (puncture-site bleeding, 5.7%; non-puncture-site bleeding, 10.2%).

## Hypotension.

With Eminase, the incidence of hypotension was 10.4%, compared to 7.9% with nonthrombolytic therapy.

## Other adverse experiences reported include:

Arrhythmia/conduction disorders; nausea and/ or vomiting; fever/chills; rash/itching. Anaphylactic reactions were rarely observed (0.2%).

\*Anderson et al. *J Am Coll Cardiol.* 1988;11:1153-1163. †Bonnier et al. *Am J Cardiol.* 1988;62:25-30. \*\*See full prescribing information.



Saves time in administration.

# EMINASE 30 U

## Saves time

In administration

Rapid preparation and administration saves critical time in initiating therapy in acute MI



Rapid initiation of therapy due to simple preparation.



IV injection for rapid use under a physician's care.



Total 30-unit dose can be completely administered in 2 to 5 minutes.

## Saving time is the first step in saving lives in acute MI

The ease of preparation and speed of administration with Eminase help reduce the critical time to initiate therapy. These valuable minutes result in optimal therapeutic effectiveness in treating the acute MI patient.

In acute MI, intervene with a single 2- to 5-minute IV injection of

EMINASE ®
ANISTREPLASE 300

Saves time in administration.

Manufactured by: **Beecham-Wülfing Neuss, West Germany** U.S. License No. 1097

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## Effect of Alteration in Loading Conditions on Both Normal and Abnormal Patterns of Left Ventricular Filling in Healthy Individuals

Thomas R. Downes, MD, Abdel-Mohsen Nomeir, MD, Kathy Stewart, RT, RDMS, Michael Mumma, MD, Richard Kerensky, MD, and William C. Little, MD

Doppler analysis of mitral flow provides a means of analyzing left ventricular (LV) diastolic function. While experimental studies have suggested that changes in left atrial pressure may affect the normal pattern of early diastolic filling, the effect of such changes on abnormal patterns of filling is unknown. Accordingly, the Doppler pattern of LV filling was analyzed in 20 subjects with LV hypertrophy (mean age  $59\pm13$  years,  $\pm$  standard deviation), in 25 healthy normal subjects ( $29\pm6$  years) and in 11 elderly subjects ( $68\pm5$  years). All underwent Doppler examination of LV inflow at rest and immediately after postural changes.

In all 3 groups, head-down positioning increased early diastolic flow velocity (E) (p <0.001), and raised the E to late diastolic flow velocity (A) ratio (p <0.01). However, an abnormal E/A ratio never approached a normal resting value. Likewise, although E and the E/A ratio decreased significantly in normal subjects with head-up positioning, it did not become abnormal. The magnitude of change in E, A and E/A ratio did not differ among the 3 groups in response to postural changes. Thus, alterations of LV loading conditions alter the pattern of LV filling, whether normal or abnormal at baseline. The magnitude of change appears to be independent of the resting flow pattern. Although loading conditions may affect the Doppler pattern of filling, simple changes in venous return do not "normalize" an abnormal pattern, nor do they "ab-normalize" a normal pattern.

(Am J Cardiol 1990;65:377-382)

oppler echocardiographic analysis of mitral flow provides a noninvasive means of analyzing left ventricular (LV) diastolic function. 1-6 Conditions that are known to impair LV relaxation are associated with a reduction in both the velocity and volume of early diastolic flow. 7-17 Thus, both a decrease in peak early transmitral flow and a relative or absolute increase in late diastolic flow have been proposed as signs of LV diastolic dysfunction.

Recent experimental studies suggest that mitral flow is determined by the instantaneous pressure difference between the left atrium and ventricle. 18-23 While disease processes that impede LV relaxation may decrease early diastolic filling by inhibiting the development of a transmitral pressure gradient, 20,24,25 changes in left atrial pressure may also affect the transmitral gradient and thus change the pattern of early diastolic filling. 3,20,22-24,26-28

Subjects with normal versus impaired LV relaxation may vary in their response to alterations in loading conditions. If so, assessment of this response may help characterize the degree of impaired relaxation present. We performed this study to determine the effect of changes in LV loading conditions on the pattern of mitral blood flow in subjects with both normal and abnormal LV relaxation.

## METHODS

Study population: The study population included 25 healthy normal volunteers with a mean age of  $29 \pm 6$ years (± standard deviation). None had a history of cardiovascular or pulmonary disease or was receiving any regular medications. Routine 2-dimensional echocardiograms were normal in all with the exception of 1 subject with mitral valve prolapse but no associated mitral regurgitation. Also included were 20 subjects with LV hypertrophy (59  $\pm$  13 years) defined as a posterior LV wall thickness >12 mm on M-mode examination who were prospectively selected from referrals to the echocardiographic laboratory at North Carolina Baptist Hospital. LV hypertrophy was concentric in all; none had hypertrophic obstructive disease. Subjects with aortic or mitral insufficiency noted on Doppler echocardiography were excluded as were subjects with aortic or mitral stenosis. Systolic LV function as assessed by 2dimensional examination was normal in all, and all were normotensive (systolic blood pressure <160 mm Hg) at the time of examination.

Lastly, 11 elderly subjects ( $68 \pm 5$  years) were included to evaluate the effects of aging on the pattern of

From the Section of Cardiology, Bowman Gray School of Medicine, Winston-Salem, North Carolina. This study was supported in part by grants in aid 1988-89-A-28 and 1989-91-A-16 from the North Carolina Affiliate, American Heart Association. Dr. Little is an Established Investigator of the American Heart Association. Manuscript received August 16, 1989; revised manuscript received and accepted September 27, 1989

Address for reprints: Thomas R. Downes, MD, Section of Cardiology, Bowman Gray School of Medicine, 300 South Hawthorne Road, Winston-Salem, North Carolina 27103.

TABLE I Responses of Doppler Parameters to Trendelenburg Positioning

	Normal		LV Hypertroph	ıy	Elderly	
	Rest	Trendelenburg	Rest	Trendelenburg	Rest	Trendelenburg
Heart rate (beats/min)	63±8	65 ± 10	69 ± 9	68 ± 10	70 ± 9	71 + 0
E (cm/s)	83 ± 9	93 ± 10*	66 ± 19	81 ± 22*	66 ± 18	71 ± 9
A (cm/s)	45 ± 9	$45 \pm 10$	79 ± 18	79 ± 22		77 ± 22*
E/A	$1.89 \pm 0.37$	2.18 ± 0.46*	$0.86 \pm 0.23$		76 ± 15	80 ± 18
E <sub>I</sub> (cm)	12.1 ± 2.9	13.3 ± 3.2*		1.06 ± 0.35†	$0.90 \pm 0.29$	$1.02 \pm 0.39^{\dagger}$
$E_{I}/T_{I}$ (%)			$10.4 \pm 3.4$	$12.3 \pm 4.2*$	$7.3 \pm 1.8$	$8.7 \pm 2.6^{\dagger}$
	$69 \pm 7$	$71 \pm 7$	$52 \pm 9$	$56 \pm 9$	$47 \pm 10$	49 ± 11
LV volume (ml)	$104 \pm 17$	$120 \pm 21^{\dagger}$	$104 \pm 28$	124 ± 30‡	$88 \pm 27$	101 ± 25

Data are mean  $\pm$  standard deviation. \*p <0.001 vs resting value; †p <0.02 vs resting value. \*p <0.001 vs resting value; †p <0.01 vs resting value; †p <0.02 vs resting value. A = late diastolic filling velocity; E = early diastolic filling velocity; E<sub>i</sub> = early flow-velocity integral; LV = left ventricular; T<sub>i</sub> = total flow-velocity integral.

TABLE II Responses of Doppler Parameters to Head-Up Positioning

	Normal		LV Hypertrophy	/	Elderly	
	Rest	Head-Up	Rest	Head-Up	Rest	Head-Up
Heart rate (beats/min)	63 ± 8	65 ± 11	69 ± 9	69 ± 9	70 ± 9	71±9
E (cm/s)	83 ± 9	68 ± 10*	66 ± 19	57 ± 16*	66 ± 18	50 ± 13*
A (cm/s)	45 ± 9	42 ± 10	79 ± 18	74 ± 18‡	76 ± 15	$70 \pm 17$
E/A	$1.89 \pm 0.37$	1.69 ± 0.39 <sup>†</sup>	$0.86 \pm 0.23$	$0.77 \pm 0.17$	$0.90 \pm 0.29$	$0.75 \pm 0.29$
E <sub>I</sub> (cm)	$12.1 \pm 2.9$	$9.7 \pm 2.6*$	$10.4 \pm 3.4$	$9.9 \pm 3.0$	$7.3 \pm 1.8$	
E <sub>1</sub> /T <sub>1</sub> (%)	69 ± 7	66 ± 8	52 ± 9	51 ± 8	$47 \pm 10$	5.9 ± 1.3*
LV volume (ml)	$104 \pm 17$	104 ± 16	104 ± 28	106 ± 31	88 ± 27	43±8 94±26

Data are mean  $\pm$  standard deviation. \*p <0.001 vs resting values; †p <0.005 vs resting values; †p <0.02 vs resting values. Abbreviations as in Table I.

LV filling. All were without coronary artery disease as proven by cardiac catheterization and none had a history of myocardial infarction or significant hypertension, and all had normal LV systolic function. We have previously reported baseline values in these elderly subjects.9

Data collection: Echocardiographic examinations were performed with Hewlett-Packard and Aloka ultrasound systems using 3.5-MHz transducers. All patients were examined in the left lateral decubitus position on a motorized tilt table. The 4-chamber apical view was used to assess mitral flow with the long axis of the left ventricle aligned vertically. With the ultrasound beam parallel to the direction of blood flow, no correction for Doppler angle was necessary. The pulsed wave sample

volume was placed just inferior to the plane of the mitral anulus within the LV cavity, and slight adjustments were made to achieve a maximal value for the peak velocity of early diastolic filling with minimal spectral dispersion. Doppler profiles and a simultaneous single-lead electrocardiogram were recorded on videotape and later digitized and analyzed using a commercially available computer system (Microsonics).

Following baseline assessment of mitral flow, subjects were tilted into a 30° Trendelenburg position by use of the motorized tilt table. Mitral flow was quickly assessed and recorded within 10 to 15 seconds, before a change in heart rate. Subjects were then returned to a level position and after return of control values were

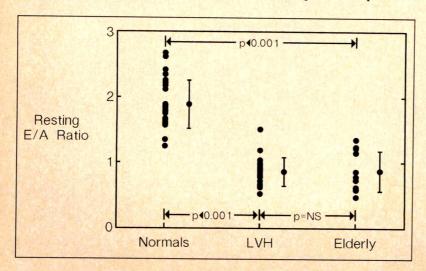


FIGURE 1. Resting E/A ratios of the 3 study groups. Note the E/A ratio is significantly lower in the left ventricular hypertrophy (LVH) and elderly subjects versus normals, indicating an impairment of early diastolic filling at rest in these 2 groups.

TABLE III Responses of Doppler Parameters to the Valsalva Maneuver

ALCOHOLD STATE	Normal		LV Hypertrophy		Elderly	
	Rest	Valsalva	Rest	Valsalva	Rest	Valsalva
Heart rate (beats/min)	61 ± 7	62±8	68±6	68±7	64 ± 5	66 ± 5
E (cm/s)	80±9	63±11	56 ± 14	53 ± 13	$71 \pm 22$	42 ± 7*
A (cm/s)	43±7	38 ± 10	73±10	$66 \pm 12$	68 ± 12	57 ± 8
E/A	1.9±0.4	$1.79 \pm 0.66$	$0.8 \pm 0.18$	$0.84 \pm 0.28$	$0.93 \pm 0.37$	$0.66 \pm 0.17$
LV volume (ml)	$1.5\pm0.4$ $104\pm17$	84 ± 19	104 ± 28	88 ± 22 <sup>†</sup>	88 ± 27	$75 \pm 31^{\dagger}$

Data are mean ± standard deviation. \* p <0.02; † p <0.01. Abbreviations as in Table I.

tilted into a 30° head-up position. Mitral flow was again assessed and recorded within 10 to 15 seconds, before a change in heart rate. The ultrasonic transducer was never moved from its original position and continuous 2-dimensional imaging allowed maintenance of the Doppler beam along the long axis of the left ventricle.

In 6 subjects from each of the 3 study populations the Valsalva maneuver was also performed, standardized at 40 cm of water with a manometer connected to a mouthpiece. In these subjects, mitral flow patterns were assessed and recorded within 5 to 10 seconds of beginning the Valsalva maneuver, after 2-dimensional imaging demonstrated a reduction in LV size but before any significant change in heart rate occurred. In these subjects, end-diastolic volume was assessed at rest, after each postural change and after the Valsalva maneuver. All images were taken from the apical 4-chamber window. End-diastolic volume was calculated off-line with a software program that uses Simpson's rule (Microson-

Data analysis: In all cases, Doppler recordings demonstrating the highest values of peak early diastolic flow, providing spectral dispersion remained minimal, were chosen for analysis. All Doppler values were calculated as the average of at least 3 cardiac cycles.

Peak early (E) and late (A) flow velocities were measured, and the E/A ratio was calculated. Flow velocity integrals for early (E<sub>I</sub>), late (A<sub>I</sub>) and total diastolic flow (T<sub>I</sub>) were calculated as well. Assuming the mitral valve orifice size remains constant during diastole,

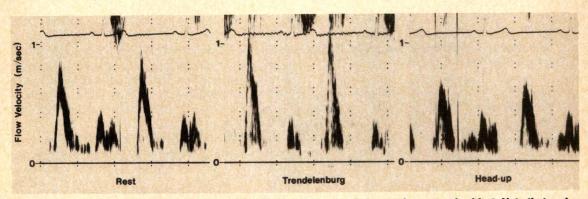


FIGURE 2. Alterations in the Doppler mitral flow pattern induced by postural changes in a normal subject. Note that early diastolic filling increases substantially with Trendelenburg positioning; opposite results are obtained with head-up positioning. Late diastolic flow velocity is relatively unaffected.

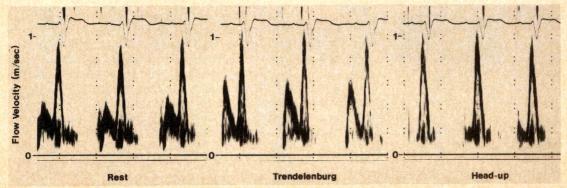


FIGURE 3. Alterations in the Doppler mitral flow pattern induced by postural changes in a subject with LVH. Note that both early and late filling velocities respond similarly to those of the normal subject in Figure 2. With head-up positioning early filling is almost abolished in this subject.

the flow integrals are proportional to the volume of blood entering the left ventricle. To assess the relative contribution of early to total diastolic flow, the ratio  $E_{\rm I}/T_{\rm I}$  was calculated.

Data were summarized as group mean  $\pm$  standard deviation. Multiple comparisons were performed by analysis of variance. When a significant effect was found integral comparisons were performed using paired t tests with correction for multiple comparisons using the Bonferroni correction.

#### RESULTS

In patients with LV hypertrophy, the resting E/A ratio (0.86  $\pm$  0.23) differed significantly from normal subjects (1.89  $\pm$  0.37, p <0.001) (Figure 1), indicating an impairment of early diastolic filling at rest. In the elderly subjects the resting E/A ratio was diminished as well (p <0.001 vs normal subjects).

In all 3 study populations Trendelenburg (headdown) positioning increased E significantly (Figures 2 and 3, Table I), while A was not significantly changed. Accordingly, the E/A ratio was significantly increased in all 3 groups (p <0.01) by head-down positioning. However, in the elderly and LV hypertrophy subjects, the Doppler E/A ratio did not approach the resting value in normal subjects. LV end-diastolic volume increased in the normal and LV hypertrophy groups.  $E_I$  increased as well, reaching statistical significance (p <0.01) in all 3 groups. However, the ratio  $E_I/T_I$  was not significantly increased in any.

A decrease in venous return, produced by head-up positioning, diminished E in all 3 subject groups (p <0.001) (Table II). The Valsalva maneuver did likewise in normal and elderly subjects (p <0.05) (Table

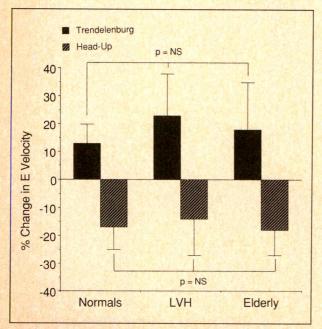


FIGURE 4. Percent change in early diastolic filling velocity with postural changes in each study group. Note that while all 3 groups demonstrate similar responses to alterations in loading conditions, the magnitude of the response does not differ significantly.

III). The E/A ratio decreased in all 3 groups with headup tilt, but reached statistical significance (p <0.005) only in the normal group. In none of the normal subjects did the E/A ratio approach the resting value seen in the elderly or LV hypertrophy groups.

Figure 4 shows the percent change in E velocity seen in each group with each maneuver. With the head-up position the accompanying percent decrease in E and E/A was significant (p <0.01). The decrease in E seen with the Valsalva maneuver was significant only in the normal subjects (p <0.001). However, when comparing degree of response to postural changes and the Valsalva maneuver among the 3 groups, no significant difference could be found.

#### DISCUSSION

This study demonstrates that in humans the Valsalva maneuver and changes in position substantially affect both normal and abnormal Doppler patterns of diastolic mitral flow, regardless of age. In normal subjects, maneuvers that diminished venous return decreased both the velocity and volume of early diastolic mitral flow, while late flow-velocity parameters were relatively unaffected. In the elderly and LV hypertrophy groups, the already abnormal pattern of LV filling was accentuated, thus giving the impression of further impairment of diastolic filling. In contrast, an increase in venous return (produced by Trendelenburg positioning) caused the opposite effect in all 3 study groups with an increase in early transmitral flow.

These data are consistent with animal studies in which volume infusion and caval occlusion have been shown to alter the velocity of early diastolic filling, independent of changes in LV relaxation. More recent clinical studies have reported that reducing venous return with nitroglycerin reduces early diastolic mitral valve flow, both in normal subjects and patients with coronary artery disease. Our study provides further evidence that in humans with normal and abnormal patterns of LV filling, as in experimental animals, left atrial pressure is also an important determinant of the atrioventricular pressure gradient after mitral valve opening.

Both the Valsalva maneuver and head-up tilt diminish venous return to the heart. In our subjects, these changes were reflected by a decrease in E. However, in all our subjects, both the velocity and volume of the atrial component of transmitral flow was unchanged. Thus, the reduction in venous return not only altered the characteristics of early diastolic flow, but also diminished its relative importance to total diastolic flow. Furthermore, in agreement with prior studies<sup>22,24,26–29</sup> these changes suggest that while early diastolic flow is dependent on the left atrial to LV pressure gradient, immediate changes in loading conditions have variable effects on later atrial-induced flow.

Although venous return is known to be inhibited by Valsalva and head-up positions, we could not demonstrate a reduction in LV end-diastolic volume, perhaps due to the brief period (seconds) involved between the initiation of each maneuver and the recording of 2-di-

mensional images. This brief interval was necessary to eliminate the effects that an increase in heart rate would have on diastolic flow patterns.

All 3 groups of subjects responded similarly to alterations of venous return with similar percent changes in E and E/A seen with each maneuver. This suggests that the response of the Doppler pattern of LV filling to changes in loading conditions is not dependent on baseline values. However, in no instance did a normal Doppler filling pattern become frankly abnormal. Likewise in the elderly and LV hypertrophy groups, an increase in loading conditions never produced an E/A ratio in the range of our normal subjects at rest. This would suggest that although the Doppler filling pattern is load sensitive, factors other than minor changes in left atrial pressure are required to make an abnormal pattern appear normal, or vice versa. Simple variations in left atrial pressure alone should not result in a false impression of normal ventricular filling in any given individual.

In this study we have chosen to define a "normal" pattern of LV filling as an E/A ratio >1; the mean value in our subjects was  $1.89 \pm 0.37$ . We have previously shown that with age this value may shift, independent of the presence of cardiac disease.9 Thus a "normal" value for the E/A ratio in elderly subjects is probably <1. However, our present data confirm that despite the change in LV filling pattern seen with aging, early filling remains equally sensitive to loading conditions.

All the subjects in our study had normal systolic function and probably had normal or near normal left atrial pressures. In some disease states (pericardial constriction, dilated cardiomyopathy) the E/A ratio may undergo "pseudonormalization" and approach the normal value.13 Thus our findings may not apply to patients with extreme elevations of left atrial pressure.

Our findings are consistent with several prior studies. Courtois et al<sup>22</sup> showed that caval occlusion in animals reduced both E and A flow velocities; hence, the E/A ratio remained relatively unchanged. Nishimura et al<sup>27</sup> showed an insignificant increase in E/A ratio with volume infusion in patients undergoing bypass surgery. Vandenberg et al<sup>26</sup> used nitroglycerin to diminish early filling in normal subjects; however, the E/A ratio decreased to a mean value of only  $1.6 \pm 0.28$ . Stoddard et al<sup>28</sup> found that the E/A ratio in normal subjects decreased to an abnormal level with nitroglycerin. However, their baseline value for "normals" was 0.94 ± 0.18, a value much lower than for our laboratory. While Appleton et al<sup>13</sup> described 12 patients with coronary artery disease and an E/A ratio exceeding that of normal subjects  $(2.6 \pm 1.1 \text{ vs } 1.5 \pm 0.4)$ , 11 had moderate to severe mitral regurgitation as evidenced by a mean pulmonary wedge pressure V wave of 36 ± 12 mm Hg. Thus only extreme changes in loading conditions have been shown to falsely correct an abnormal E/A ratio. Normal patterns have not been shown to become abnor-

While theoretically possible, it is unlikely that alterations in the diastolic properties of the left ventricle were involved in producing the changes noted in our

subjects. It is unlikely that simple physiologic maneuvers had an effect on LV relaxation in the 10 to 15 seconds before the recording of Doppler signals. Therefore, with the rate of LV pressure drop remaining relatively constant, only alterations in left atrial pressure would be expected to reduce or enhance transmitral flow.

Careful attention to technical details of the echocardiographic examination helped to ensure accuracy of our Doppler measurements. Although changes in posture may have changed the orientation of the heart and therefore the Doppler angle, this effect was minimized by repositioning the sample volume to seek out maximal signals. Continuous 2-dimensional imaging allowed maintenance of the Doppler beam perpendicular to the mitral anulus.

Alterations in heart rate have been shown to change the pattern of transmitral flow.<sup>29-31</sup> However, conflicting data exist regarding the magnitude of change necessary to alter the dynamics of mitral flow significantly. After initiation of each physiologic maneuver in our study, mitral flow values were assessed and recorded before substantial changes in heart rate occurred. Changes that did occur were not significant.

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# Accuracy of Digital Holter Monitoring of Extent and Duration of Ischemic Episodes Compared to Analog Recording

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Analog amplitude-modulated Holter devices are in widespread use for arrhythmia detection, but their reliability remains questioned for ST-segment analysis. In contrast, recently developed digital Holter devices immediately digitize and analyze the electrocardiogram (ECG) on-line and may therefore be more reliable for ST-segment analysis. To test this hypothesis, the results of digital, on-line, 2-channel ST-segment analysis were directly compared to those of analog amplitude-modulated recordings in identical leads (CM5 and CM3), using a stripchart recorder meeting the American Heart Association specifications as the standard. Thirty-five patients (25 with coronary artery disease and 10 control subjects) underwent graded treadmill exercise testing. The reference ECG mean value for ST-segment depression in CM<sub>5</sub> was  $-1.4 \pm 1.2$  mm and in CM<sub>3</sub>  $-0.5 \pm 1.2$  mm. For digital analysis, the mean values and correlation coefficients for CM<sub>5</sub> were -1.5  $\pm$  1.1 mm (r = 0.97) and for CM<sub>3</sub> -0.8  $\pm$  1.3 mm (r = 0.93). For analog recording, the results for CM<sub>5</sub> were  $-2.1 \pm 1.7$  mm (r = 0.88) and for CM<sub>3</sub>  $-1.3 \pm 1.9$  mm (r = 0.85). The mean duration of ST-segment depression with the reference ECG was 7.1  $\pm$  4.1 minutes. Digital Holter showed a significantly better agreement (7.4  $\pm$  4.4 min, r = 0.97) than analog Holter (9.6  $\pm$  5.6 min, r = 0.84). Because analog amplitude-modulated Holter recordings overestimated the degree and duration of ischemic episodes, digital, on-line and full disclosure devices should be preferred to assess myocardial ischemia.

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ith the recognition that episodes of myocardial ischemia are frequently asymptomatic, the use of Holter monitoring1 to assess the "total ischemic burden" of patients with coronary artery disease has become increasingly important.2 ST-segment Holter monitoring is clinically useful in patients with angina pectoris to assess the efficacy of antiischemic therapy during daily activities and for prognostication.3-Analog amplitude-modulated Holter devices are in widespread use for arrhythmia detection, but their reliability remains questioned for ST-segment analysis.8-12 Analog amplitude-modulated devices are inherently limited by signal distortion due to their need for recording on and replaying from magnetic tape. In contrast, recently developed digital Holter devices immediately digitize and analyze the electrocardiogram (ECG) with microprocessors and may therefore be more reliable for ST-segment analysis. The recently published American College of Cardiology/American Heart Association Task Force on Ambulatory Electrocardiography report attributes to digital Holters "primary advantages due to elimination of mechanical parts and improvement of signal to noise ratio." 13 However, digital Holters have been criticized because of the "unproved ability of the available algorithms to analyze ST-segments." 14 To test the hypothesis that digital Holter recording is more reliable than analog amplitude-modulated recording, we compared the results of digital, on-line, 2-channel (CM<sub>5</sub> and CM<sub>3</sub>) ST-segment analysis directly to those of analog amplitude-modulated recordings in identical leads, using a stripchart recorder that meets the American Heart Association specifications as the standard.

### **METHODS**

Thirty-five patients were enrolled. Twenty-five had coronary artery disease with known exercise-induced ST-segment depression and 10 had no evidence of coronary artery disease and a normal treadmill test result. Further inclusion criteria were sinus rhythm, no resting ST-segment depression or conduction disturbances and no digitalis therapy. A symptom-limited graded treadmill exercise test was performed using the standard Bruce protocol (Burdick T500 treadmill/ExTol 700 stress system).

After skin abrasion, silver/silver chloride electrodes were attached in CM<sub>5</sub> and CM<sub>3</sub> locations. For the reference ECG, an ESAOTE Biomedica 3-channel stripchart recorder with a frequency response of 0.05 to 100 Hz at -3 dB, meeting the US (AAMI EC11) and Eu-

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**TABLE I** Sensitivity and Specificity for Detection of ST-Segment Depression by Digital and Analog Holter Recordings in Leads CM<sub>5</sub> and CM<sub>3</sub>

ALLEGO DAY CONTACT AND ASSESSMENT			
	CM <sub>5</sub>	CM <sub>3</sub>	$CM_5 + CM_3$
Pts with ST-segment depression on the reference electrocar- diogram (n) Sensitivity (%)	24	15	25
Digital Holter Analog Holter Pts without ST-segment depression on the reference electrocar- diogram (n) Specificity %	23/24 (96) 24/24 (100) 10	15/15 (100) 15/15 (100) 10	25/25 (100) 25/25 (100) 10
Digital Holter Analog Holter	9/10 (90) 6/10 (60)	9/10 (90) 7/10 (70)	9/10 (90) 6/10 (60)

ropean (IEC62D, C06) standards, was chosen. It was attached together with the Holter recorder using split leads to CM<sub>5</sub> and CM<sub>3</sub>, so that identical leads were simultaneously seen by both devices. A high fidelity external signal was used for calibration of the reference ECG and the Holter ECG (1 mm = 0.1 mV).

We used the Oxford Medilog-4500 with MR 45 recorders (Oxford Medical Ltd.) because it represents an innovative link between digital on-line analysis and analog AM recording in 1 device.

The on-line component has a frequency response of 0.06 to 70 Hz at -3 dB. There are 32,000 bytes of memory for digitizing the ECG, with a sample rate of 128 Hz. The isoelectric line is automatically measured at 56, 64 and 72 ms before the R wave ("fiducial point"), the ST segment at 96, 104 and 112 ms after the R wave. An averaging algorithm is then applied to both measurements with weighting factors of 1:2:1. Both

channels are simultaneously analyzed. The software excludes arrhythmias as well as noisy beats from ST-segment measurements. Digital numbers were directly obtained from the automatic printout.

The analog component is a traditional amplitude-modulated recording/replay unit with a frequency response of 0.08 to 60 Hz at -3 dB. To compare the analog tracings to the digital ST-segment measurements, the isoelectric line was determined 60 ms before the peak of the R wave and the ST-segment at 100 ms after the R wave. ST-segment measurements were averaged by taking 5 consecutive heart beats at peak exercise.

The magnetic tape records the information for both the analog and the digital components. Two of the 4 tracks are used for continuous analog 2-channel registration of the ECG, enabling retrospective analysis of each single heart beat. A third track stores the online continuous digital ST-segment analysis. The fourth track records the time markers.

The stripcharts were recorded at 25 mm/s. The reference ECG was synchronized to the Holter device and ST-segments were determined at peak exercise. The reference and analog ST-segment measurements were made in identical fashion, and independently by 2 observers. In case of disagreement, consensus was achieved.

An abnormal episode was defined as ≥1 mm of ST-segment depression for at least 1 minute. The sensitivity and specificity of the Holter to detect or exclude ST-segment depression was based on the reference ECG. The duration of an ischemic episode was determined in the lead with the greater ST depression.

**Statistical analysis:** The results are expressed as mean  $\pm 1$  standard deviation. Linear regression analysis was performed and characterized by the estimated

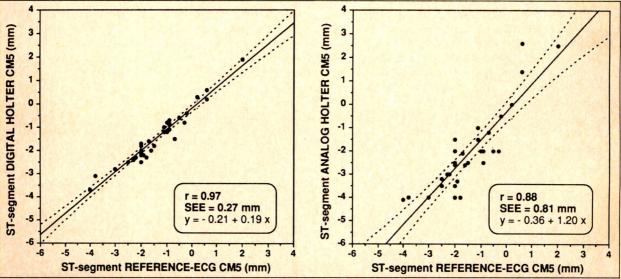


FIGURE 1. Correlation coefficients (r), standard error of the estimates (SEE) and estimated equations for linear regression analysis between ST-segment measurements by the reference ECG versus digital Holter (*left*) and analog Holter (*right*) in lead CM<sub>5</sub>. The solid line represents the regression line, and the dashed line the upper and lower 95% confidence limits. The digital analysis correlated significantly better with the reference ECG than the analog recording.

equations, correlation coefficients and standard error of the estimates. The significance of the linear regression analysis was tested with the usual F statistic, and t tests for the equality of the slope to unity and the intercept to 0 (the line of identity) were performed. The Fisher test for homogeneity of correlation coefficients was used to compare the regression analysis of the analog and digital recordings. The chi-square test was used to compare sensitivity and specificity. A p value <0.05 was considered to be significant.

### RESULTS

Reference electrocardiogram: According to the inclusion criteria, all 25 patients with coronary artery disease had an abnormal exercise-induced ST-segment depression in CM<sub>5</sub> or CM<sub>3</sub> of the reference ECG. Lead CM<sub>5</sub> alone revealed an abnormal ST-segment depression in 24 of 25, and lead CM<sub>3</sub> in 15 of 25 patients. The combination of both leads resulted in an abnormal ST-segment depression in all 25 patients (Table I). As also required by the inclusion criteria, neither lead CM<sub>5</sub> nor lead CM<sub>3</sub> of the reference ECG showed an abnormal ST-segment depression in the 10 control patients (Table I).

The mean value for all ST-segment measurements in  $CM_5$  was  $-1.4 \pm 1.2$  mm and in  $CM_3 -0.5 \pm 1.2$  mm. The mean duration of transient episodes of ST-segment depression was  $7.1 \pm 4.1$  minutes.

**Digital Holter:** Using the reference ECG as standard for ST-segment depression, digital Holter resulted in a sensitivity of 96% (23 of 24) for CM<sub>5</sub> and of 100% (15 of 15) for CM<sub>3</sub> (Table I). The combination of lead CM<sub>5</sub> and CM<sub>3</sub> showed a sensitivity of 100% (25 of 25). The specificity for CM<sub>5</sub> as well as for CM<sub>3</sub> was 90% (9 of 10) with a combined (CM<sub>5</sub> and CM<sub>3</sub>) specificity of 90% (9 of 10, Table I).

The mean value for all ST-segment measurements in  $CM_5$  was  $-1.5 \pm 1.1$  mm and in  $CM_3 -0.8 \pm 1.3$  mm. There was no significant difference between the mean values of the digital Holter and the reference electrocardiogram in  $CM_5$  or  $CM_3$ .

The correlation coefficient between the digital measurements and the reference ECG was r = 0.97 with a standard error of the estimate of 0.27 mm for CM<sub>5</sub> (Figure 1) and r = 0.93 with a standard error of the estimate of 0.47 mm for CM<sub>3</sub> (Figure 2). For both regression lines, the inclination and the intercepts with the y axis were not significantly different from the line of identity (Figures 1 and 2).

The mean duration of the episodes of transient episodes of ST-segment depression was  $7.4 \pm 4.4$  minutes, which was not significantly different from the reference ECG. The correlation coefficient between the duration of transient ST-segment depression as determined with digital Holter and that from the reference ECG was 0.97 with a standard error of the estimate of 1.1 min (Figure 3).

Analog Holter: Based on the ST-segment depression on the reference ECG, analog Holter resulted in a sensitivity of 100% for CM<sub>5</sub> (24 of 24) as well as for CM<sub>3</sub> (15 of 15, Table I). The specificity for CM<sub>5</sub> was 60% (6 of 10) and for CM<sub>3</sub> 70% (7 of 10). The combination of CM<sub>5</sub> and CM<sub>3</sub> revealed a specificity of 60% (6 of 10, Table I).

The mean value for all ST-segment measurements in  $CM_5$  was  $-2.1 \pm 1.7$  mm and in  $CM_3 -1.3 \pm 1.9$  mm. The mean values for  $CM_5$  as well as those for  $CM_3$  were significantly different from the corresponding values on the reference ECG.

The correlation coefficient between the analog measurements and the reference ECG was 0.88 with a standard error of the estimate of 0.81 mm for CM<sub>5</sub> (Figure

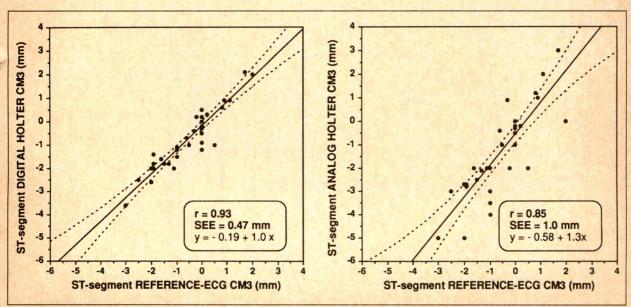


FIGURE 2. Comparison between ST-segment measurements by the reference ECG versus digital Holter (left) and analog Holter (right) in lead CM<sub>3</sub>. This lead also showed a significantly better correlation between digital analysis and the reference ECG than the analog recording. Symbols and abbreviations as in Figure 1.

1) and 0.85 with a standard error of the estimate of 1.0 mm for CM<sub>3</sub> (Figure 2). For both regression lines, the inclination and the intercepts with the y axis were not significantly different from the line of identity (Figures 1 and 2).

The mean duration of the episodes of transient episodes of ST-segment depression was  $9.6 \pm 5.6$  minutes and significantly longer than the duration determined from the reference ECG. The correlation coefficient of the duration of ST-segment depression with analog Holter compared to reference ECG was 0.84 with a standard error of the estimate of 3.1 minutes (Figure 3).

The comparison of the sensitivity and specificity of the analog and digital recordings showed a significantly higher specificity for the digital technology (Table I). Also the regression analysis revealed significant differences for the amount of ST segment in CM<sub>5</sub> (Figure 1), CM<sub>3</sub> (Figure 2) and duration of ischemia (Figure 3).

### **DISCUSSION**

As our results show, digital Holter monitoring is more reliable for the assessment of extent and duration of transient myocardial ischemia than analog amplitude-modulated recording. Analog amplitude-modulated systems, which represent the vast majority of the Holters used for arrhythmia detection, have been substantially criticized regarding their reliability to detect ST-segment changes. 8-11 Our results, of course, apply only to the system tested, but even recently developed amplitude-modulated systems with newer technology have shown limited value for ST-segment analysis. 12

Laboratory tests: Characteristically, several laboratory parameters, such as frequency response and phase shift, have been used to describe the electric properties of Holter devices.

An inadequate frequency response distorts the ECG by inconsistent degrees of amplification of its different frequency components. In 1975, the American Heart Association recommended a standard frequency response of 0.05 to 100 Hz at -3 dB for faithful recording with bedside electrocardiographs. However, in 1982, Bragg-Remschel et al 11 tested equipment from 8 Holter manufacturers and noted that none of the recorder plus replay units met the American Heart Association standard.

An inadequate phase response may delay low frequencies of the QRS complex and make them appear in the ST segment, causing artifactual changes resembling those seen in ischemic heart disease. Initially, the American Heart Association recommendations did not mention the phase response.<sup>17</sup> In the subsequent years, considerable phase distortions (60 to 150°) have been detected in a number of systems.<sup>11</sup> Consequently, the American Heart Association added the standard of a linear phase response from 0.05 Hz to 60 Hz.<sup>18</sup> Using digital analysis, phase distortions should not be expected.<sup>14,19,20</sup>

There is a complex interaction between amplitude and phase response. This became more evident from a study by Lambert et al,<sup>21</sup> showing that the American Heart Association's minimum frequency response criteria do not apply when using a high fidelity instrument with a flat frequency response and no measurable phase shifts. Therefore, the "ideal" electrocardiograph should have a flat amplitude (i.e., all components equally amplified) and a linear phase response (i.e., all components equally delayed) between 0.5 Hz and 60 Hz.<sup>12</sup>

In contrast to analog amplitude-modulated units, analog frequency modulated units are accepted for faithful reproduction of ST-segment shifts. 11,22 Because

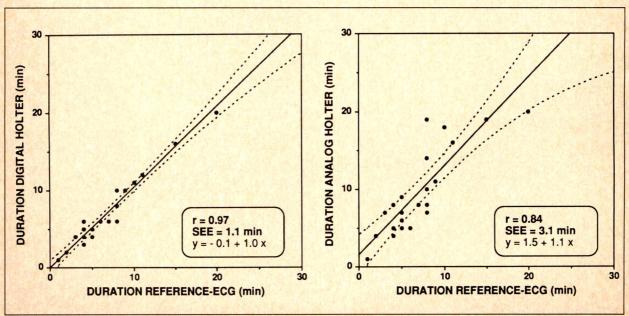


FIGURE 3. Duration of exercise-induced ST-segment depression as determined by digital analysis (*left*) and analog recording (*right*) compared with the reference ECG. The digital analysis correlated significantly better with the reference ECG than the analog recording. Symbols and abbreviations as in Figure 1.

these frequency-modulated devices, however, are rarely used clinically, we preferred to compare digital recording to the overwhelmingly used amplitude-modulated technology. In addition, because it has been suggested that the accurate assessment of the ischemic status of patients requires a total recording of 72 hours,23 the reading of so many tapes would be time consuming and subject to interobserver variability. For frequency-modulated tapes, a retrospectively computerized reading has been developed, but is not generally available.<sup>22</sup>

Since "the exact effect of amplitude and phase distortion is difficult to predict," electronically simulated ECGs have been used to validate ST-segment Holter monitoring.<sup>11</sup> These synthesized signals, however, may contain different frequencies compared to real, patient-generated signals.<sup>21</sup> Therefore, electronic laboratory studies alone are not sufficient to predict the accuracy of ST-segment measurements, especially in a noisy pa-

tient environment such as during exercise.

Patient evaluation: We used the clinical approach, recording real, patient-generated signals. To reference the Holter results to an electrocardiograph meeting the American Heart Association standards, we chose the treadmill test as the model to induce transient myocardial ischemia. It is important to emphasize that we registered the Holter and reference ECGs from identical leads, which is essential for validation purposes. 24,25 Others have used patient-generated signals, however, registering from different leads for recording of Holter and reference ECG, which makes a direct comparison difficult.20,26

The high sensitivity and specificity found in this study should not be confused with those reported for Holter monitoring to detect coronary artery disease. 19 Our data were related to the detection of ST-segment changes compared to identical leads on the reference ECG (Table I). Of course, with Holter monitoring, the issue of false-positive ST-segment shifts remains. Therefore, ST-segment changes in patients without known coronary artery disease must be interpreted with cau-

For ambulatory monitoring, only bipolar leads are available. Chaitman et al<sup>27</sup> have shown that the bipolar, frontal lead CM<sub>5</sub> is more sensitive, but less specific than the unipolar, horizontal V<sub>5</sub>. There is no doubt that the sensitivity of a single lead to detect myocardial ischemia can be increased by the addition of multiple leads. Accordingly, compared to CM<sub>5</sub> alone, the addition of CC<sub>5</sub> increased the sensitivity by 9 to 17%27-29 and the addition of CM<sub>3</sub> by 7%.<sup>26</sup> The combined use of CM<sub>5</sub> and CM<sub>3</sub> had the same sensitivity and specificity for the detection of coronary artery disease as the standard 12 leads.<sup>26</sup> The addition of a third bipolar lead may additionally increase the diagnostic information.<sup>30</sup>

Clinical impact: The digital Holter system tested in this study accurately detects extent and duration of transient ST-segment changes. Digital Holter devices are reliable and their on-line, fully automatic measurement of ST-segment shifts make them suitable for widespread and repeated applications. 19,20 Because analog amplitude-modulated recordings appear to overestimate the degree and duration of ischemic episodes, digital, on-line and full disclosure devices should be preferred to assess myocardial ischemia with Holter monitoring.

Acknowledgment: We appreciate the technical assistance of Lucia Sanderson and gratefully thank Thomas L. Sheffield, MD, for critically reviewing the manuscript.

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### **Mechanism of Directed Transluminal Atherectomy**

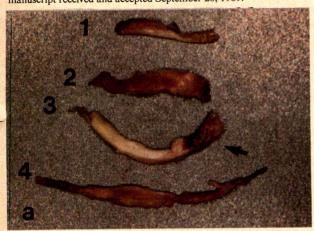
Danna E. Johnson, MD, Lissa Braden, BS, and John B. Simpson, MD, PhD

irected transluminal atherectomy is a new catheter-mediated technique for the treatment of symptomatic peripheral and coronary artery atherosclerosis.1 Unlike angioplasty, which may improve vessel patency by disrupting the plaque and stretching the arterial wall, the Simpson atherectomy catheter was specifically designed for percutaneous resection and removal of atherosclerotic plaques. 1-3 It was hypothesized that such an approach would allow for more predictable clinical results with fewer acute complications compared to balloon angioplasty. In the current study, the mechanism of directed atherectomy was investigated through experimental procedures performed on diseased segments of human arter-

The Simpson atherectomy catheter (Devices for Vascular Intervention) has a distal cylindrical housing with a longitudinal opening within which is located a motordriven, rotating cutting element. A hollow chamber at the distal end of this housing serves as a storage receptacle for excised pieces of tissue. Along the closed border of the housing lies an inflatable balloon that is used to stabilize the device across a stenosis.

Experimental atherectomy using 9Fr and 11Fr catheters was performed on 73 unopened, fresh, 2 to 4 cm

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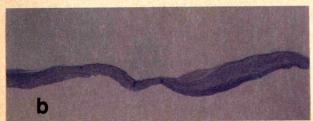


FIGURE 1. A, strips of atherosclerotic plaque removed by atherectomy measuring 0.5 to 1.4 cm in length. Cut surfaces are shown for specimens 2 and 4, and luminal aspect for specimens 1 and 3. Organizing surface thrombus is present on sample 3 (arrow). B, fibrous plaque excised by experimental atherectomy (Masson's trichrome, magnification  $\times$  3.3).

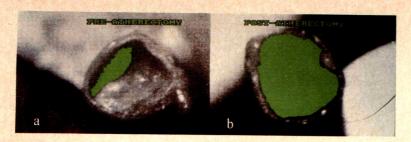
long segments of atherosclerotic human arteries dissected from cadavers or lower extremity amputations. Nine external iliac, 45 superficial femoral, 4 tibial, 12 coronary and 3 renal artery segments were used. The crosssectional luminal area of most arteries was narrowed by 50 to 75% due to eccentric plaques, as assessed by visual inspection. The procedure involved insertion of the atherectomy catheter oriented so that the cutter faced the grossly visible plaque. The support balloon was inflated to low pressures, usually 15 to 30 ψ, with slight external manual pressure applied rarely to large vessels if a snug fit was not achieved by support balloon inflation alone. The rotating cutter was then activated and advanced slowly forward 1 or more times. In many cases the balloon was deflated and the position of the cutter changed slightly to permit resection of greater plaque volume.

Following balloon deflation and withdrawal of the device, the tissues were removed from the collection chamber and examined and measured under a dissecting microscope. Arteries and excised tissues were fixed in 10% buffered formalin and decalcified in acid (0.1% hydrochloric acid and 0.7% ethylenediaminetetraacetic acid) when needed. Serial cross-sections of treated arteries and longitudinal sections of the retrieved plaque





FIGURE 2. A, photomicrograph of a superficial femoral artery showing a U-shaped trough (arrow) cut into fibrous cap and lipid core of plaque by a single pass (Masson's trichrome, original magnification  $\times$  4). B, the cut margin is smooth (Masson's trichrome, original magnification  $\times$  20).



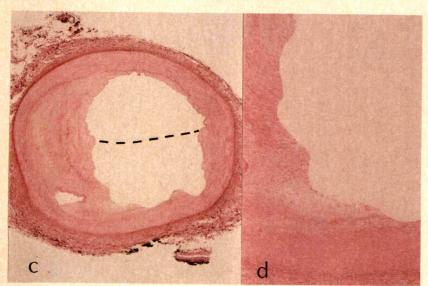


FIGURE 3. A, an eccentric plaque within a coronary artery before atherectomy. B, after atherectomy, most of plaque was excised. A and B show area plotted by photometric topography. C, multiple passes have removed about 50% of this eccentric plaque. Dotted line shows approximate original lumen (hematoxylin and eosin, original magnification × 2). D, cut border is smooth, with a scalloped contour (arrows) (hematoxylin and eosin, original magnification × 16).

specimens were prepared (5 µm thick), and stained with hematoxylin and eosin, Masson's trichrome and elastic van Gieson stains.

Atherectomy consistently removed strips of tissue, leaving behind grossly visible linear troughs cut into the atherosclerotic plaques. Small ridges within these troughs were occasionally observed under the dissecting microscope and were probably caused by the rotational movement of the cutter. The size of resected samples ranged from 2 mm long × 1 mm wide × 0.5 mm deep to 15 mm long × 2 mm wide × 1.5 mm deep. Most speci-

FIGURE 4. Three passes at the same location have produced a defect (*small arrow*) within this superficial femoral artery that extends focally into the media (*wide arrow*) (hematoxylin and eosin, original magnification  $\times$  2).

mens were at least 4 mm in length. Recovered tissues were whitish tan in color, often with bright yellow regions corresponding to areas of high lipid content (Figure 1A). Reddish brown surface thrombus and hard calcific nodules were occasionally noted grossly.

A total of 278 strips of tissue were excised from the 73 arterial segments. The excised strips of tissue microscopically were portions of atherosclerotic plaque (Figure 1B), often with organizing surface thrombus and intraplaque hemorrhage. Severely calcified samples tended to be smaller and more irregular than noncalcified specimens. Typically, the proximal ends of samples were thinner and more tapered than the distal ends, which were rounded or squared-off. The deep cut surfaces were usually smooth and fairly straight. Despite loss of the endothelium, the luminal aspect of samples could usually be distinguished from the cut margin. The luminal borders consisted of continuous bundles of collagen whereas the collagen along the deep cut edges appeared transected and disrupted. Some arterial media were present at the base of 56 (21%) of the 278 specimens and adventitia along 4 (1%) samples.

Microscopic changes attributable to atherectomy were present in all treated arteries. Total or near total loss of the endothelium was a constant finding, both along the cut surfaces and the zones that had been in contact with the inflated support balloon. Single passes with the cutter produced concave U-shaped defects with smooth and regular borders (Figure 2). Multiple passes at adjacent sites created wider and deeper defects, the size of which depended on the quantity of plaque removed (Figure 3A and B). The borders of these cuts often appeared scalloped yet they showed little fraying

or fragmentation of the residual plaque (Figure 3C and

Sequential cuts at the same location usually extended well into the lipid cores of atheromas and sometimes penetrated the media or adventitia (Figure 4). Perforations, however, were exceedingly rare. Perforation occurred only when the attenuated wall that resulted from numerous previous passes was deliberately forced into the path of the cutting element by external manual pressure. Without this direct pressure the compliant media and adventitia layers tended to stretch outward and away from the advancing cutter.

Small cracks within or focally undermining atherosclerotic plaques were observed in 48 (66%) of the arteries. These splits caused partial dehiscence of the plaque from the underlying internal elastic lamina but did not extend into the media. In general, the largest splits were encountered in coronary and tibial arteries with calcified, high grade stenoses. Some of these segments had been treated using oversized devices. Although mild vessel stretching was sometimes observed during the atherectomy procedure, no histologic evidence of wall stretching was noted.

This histopathologic study has confirmed the proposed mechanism and potential efficacy of directed percutaneous atherectomy. The Simpson atherectomy device can reliably remove strips and pieces of stenosing plaque from diseased artery segments. The degree of resultant luminal enlargement appears to be a function of the quantity of tissue excised and, with multiple serial passes, it is possible to nearly completely resect stenoses.

Eccentric lesions are as amenable to atherectomy as concentric stenoses, probably because the cutting element can be specifically directed toward the plaque. Fibrous plaques, atheromas and thrombi are all readily retrieved by the device. Heavily calcified lesions offer greater resistance to cutting but, with persistence, most can be excised with capture of all the calcific debris within the distal collection chamber.

Atherectomy creates confluent, concave defects within the treated plaque that usually have smooth, regular cut borders. Occasionally, cuts extend into the media or inner portion of the adventitia. However, we were not able to produce any vessel perforations unless the artery wall was intentionally forced into the path of the rotating cutter by external compression. In clinical practice, arterial perforation has occurred extremely rarely (2 coronary atherectomy cases, unpublished data), despite the presence of media and adventitia along the base of plaque specimens from up to 14% of treated stenoses.<sup>1,4</sup>

Some cross-sections of treated cadaver and amputation arteries revealed small cracks within and undermining plaques, somewhat reminiscent of changes observed after angioplasty. <sup>2,3,5</sup> However, most of these fissures were probably artifacts and not produced by the atherectomy device itself. Similar artifacts have been noted in cross-sections of diseased cadaver arteries that have not been treated by any intervention. <sup>6</sup> Nonetheless, we cannot exclude the possibility that a small Dotter or angioplasty effect may sometimes accompany atherectomy, particularly at high grade narrowings. Although plaque distortion created in this fashion might increase the luminal area slightly, the major mechanism of directed transluminal atherectomy is plaque removal.

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## Reproducibility and Circadian Rhythm of Heart Rate Variability in Healthy Subjects

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ow heart rate (HR) variability, expressed as the standard deviation of cardiac cycle lengths, has been shown to be associated with increased mortality in patients with coronary artery disease. HR variability can be easily measured from 24-hour electrocardiographic recordings using recently developed software. How-

ever, reference values for HR variability and their reproducibility in normal persons are not well studied. We estimated the reproducibility and circadian rhythm of HR variability, measured from repeated 24-hour electrocardiographic recordings, in young healthy adults to establish normal values and determine patterns of reproducibility.

Twenty-two normal volunteers participated in the study (Table I). Eleven subjects underwent three 24-hour ambulatory electrocardiographic recordings on 2 consecutive days and then again for another 24 hours 1 week later. The other 11 subjects underwent two 24-hour recordings; 4 on 2 consecutive days and 7 at 1-week

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No.	Age (yrs),	24-Hour Average HR Variability (ms)				24-Hour Average HR (beats/min)				
	Sex	Day 1	Day 2	Day 7	CV (%)	Day 1	Day 2	Day 7	CV (%)	
1	35, M	82	75	77	5	62	69	63	6	
2	27, M	106	97	_	6	66	68		2	
3	37, F	71	71	70	1	78	80	79	1	
4	40, F	55		58	4	81		79	2	
5	31, F	45	44	65	23	92	93	82	7	
6	32, M	92	90	72	13	76	75	83	6	
7	25, F	49	56	51	7	91	87	92	3	
8	38, M	55	63	67	10	90	87	83	4	
9	38, M	32	31		2	97	101		3	
10	30, F	59	64		6	79	76		3	
11	20, M	74		71	3	90		92	2	
12	23, F	65		65	0	90		84	5	
13	29, F	61	67	63	5	90	84	89	4	
14	31, M	87	82	87	3	74	72	72	2	
15	32, M	53		57	5	81	14 25 60	80	1	
16	35, M	58		71	14	63	_	82	19	
17	34, M	63		81	18	78		63	15	
18	30, M	56	58	55	3	82	67	66	13	
19	26, F	52	53	59	7	85	84	79	4	
20	35, M	84	88		3	70	67		3	
21	29, M	74	79	70	6	72	70	74	3	
22	31, M	93	96	102	5	55	55	54	1	

intervals. Electrocardiographic recordings continued for 24 hours while the subjects undertook their normal work and leisure activities.

Two-channel 24-hour ambulatory electrocardiographic recordings were analyzed by a Delmar Avionics Innovator 750 with previously validated supplemental software for postprocessing analysis of HR variability. The software calculated the standard deviation of cardiac cycle lengths for normal sinus beats during successive 5-minute intervals over the course of the 24-hour monitoring period. All ectopic complexes were excluded from the analysis, as were 5-minute intervals with <30 evaluable sinus beats. The mean and standard deviation of the cardiac cycle lengths were calculated for 5-minute intervals. The average HR variability and the average HR were determined for each 1-hour period and for the 24-hour period.

The paired t test was used to compare the hourly average HR variability and the average HR between different times of the day. Reproducibility was estimated by determining the coefficient of variation for repeated 1-hour and 24-hour average HR variability and HR. Data are expressed as mean ± standard deviation.

The average 24-hour HR variability and the average HR recorded and calculated for each subject are listed in Table I. The mean 24-hour average HR variability for the whole group was  $68 \pm 16$  ms (range 32 to 102; interindividual coefficient of variation 24%), and the mean heart rate was  $79 \pm 10$  beats/min (range 55 to 99; interindividual coefficient of variation 13%). The mean intraindividual coefficient of variation for the 24-hour average HR variability between repeated recordings was  $7 \pm 6\%$  and for the HR  $5 \pm 5\%$ . A negative correlation existed between the 24-hour average HR variability and

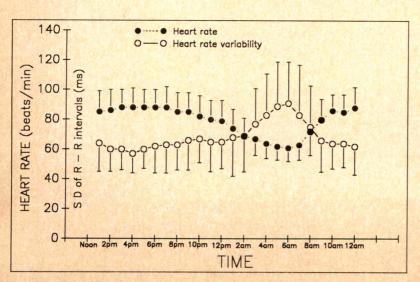


FIGURE 1. The circadian rhythm of heart rate variability and heart rate in healthy young adults. Values are mean ± standard deviation.

the average HR (r = -0.75, p < 0.001). The mean hourly HR variability and HR for the entire group are shown in Figure 1. Significant intraindividual variation occurred in hour-to-hour HR variability (mean coefficient of variance  $23 \pm 10\%$ ) exceeding the hourly variation of the average HR (mean coefficient of variance  $15 \pm 3\%$ ) (p < 0.01). HR variability started to increase and HR to decrease during the sleeping hours. The maximum HR variability occurred within 3 hours before waking up on all recordings and the minimum HR within 4 hours. The average 1-hour HR variability decreased from  $94 \pm 28$  to  $68 \pm 20$  ms (p < 0.01) after waking up and the average HR increased from  $67 \pm 5$  to  $84 \pm 11$  beats/min (p < 0.001).

Previously, several simple tests have been used to estimate cardiac autonomic function.3-5 However, variability of individual results has been observed when measurements are made over a very short time span, perhaps because of the natural circadian and hour-to-hour variation of autonomic tone. The average 24-hour HR variability was generally well reproducible within subjects, demonstrating the usefulness of this index in assessing cardiac autonomic tone and in evaluating the effects of different interventions on autonomic function. However, significant interindividual variation was found in HR variability, suggesting that there are marked intersubject differences in the magnitude of fluctuations in cardiac autonomic tone in healthy subjects. Less intersubject and intrasubject variation was found in the HR than HR variability. HR variability is predominantly influenced by cardiac vagal activity, while HR is also influenced by sympathetic activity.<sup>6</sup> Large temporal variability seems to occur in vagal tone, which is reflected as abrupt changes in HR variability but as smaller changes in HR.

A reproducible circadian rhythm of HR variability was observed in normal subjects with a maximum occurring early in the morning before waking up, reflecting high vagal tone at that time. The HR variability decreased abruptly during the hours after waking, perhaps because of inhibition of the parasympathetic cardioinhibitory center at the time of waking. Further studies may provide more information about the circadian fluctuations of cardiac autonomic tone and their relation to cardiovascular events in patients with various heart diseases.

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### Utility of a Stimulus Artifact Suppressor for Transesophageal Pacing

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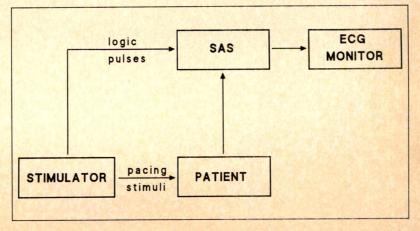
Successful transesophageal pacing requires stimuli of 10 ms duration and 10 to 20 mA.<sup>1,2</sup> Consequently, potentials of ≥20 V develop in the esophagus. The resulting stimulus artifacts obscure the surface electrocardio-

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graphic (ECG) records since they exceed the dynamic input range of the typical ECG recorder. This report describes the utility of a stimulus artifact suppressor (SAS) in 20 patients undergoing electrophysiologic evaluation with transesophageal pacing. The SAS utilizes sample and hold circuits placed between the patient and the ECG recorder.

We evaluated 20 patients aged 1 day to 25 years. Electrophysiologic diagnosis included primary atrial

FIGURE 1. Diagram of connection of stimulus artifact suppressor (SAS), stimulator, patient and electrocardiographic monitor.



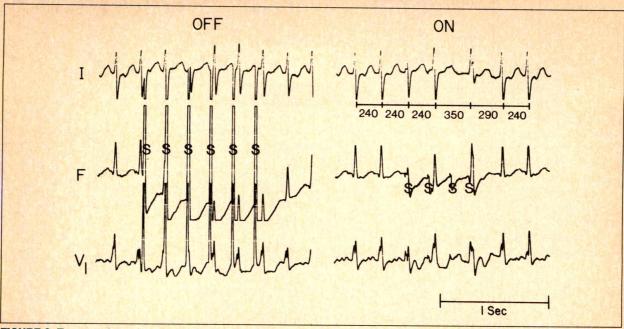


FIGURE 2. Transesophageal pacing during supraventricular tachycardia (orthodromic reciprocating tachycardia). On the left (OFF), the stimulus artifact during burst pacing with 6 stimuli (S) produces marked distortion of the surface electrocardiogram, and it is difficult to ascertain why pacing was unsuccessful in achieving tachycardia conversion. On the right (ON), burst pacing is again unsuccessful in achieving tachycardia conversion. However, because the SAS diminishes the stimulus artifact, it is possible to determine from the changes in the RR intervals that pacing terminates tachycardia (probably after second stimulus), but then reinitiates tachycardia (probably after third stimulus).

tachycardia<sup>3</sup> (4 patients), ventricular tachycardia (2 patients), tachycardia due to reentry within the atrioventricular node and orthodromic reciprocating tachycardia (11 patients). Wolff-Parkinson-White syndrome was present in 6 of the latter patients. Transesophageal pacing used stimuli with pulse widths of 10 ms and <20 mA. Bipolar electrodes with 15 mm (catheter) or 14 mm (pill) spacing were used. ECG leads I, F and V<sub>1</sub> were monitored.

The SAS is optically isolated from the stimulator and has input defibrillation protection. The electrical isolation between the SAS and the stimulator ensures that no inadvertent skeletal muscle stimulation occurs due to ground-seeking pacing current through a surface electrode. The SAS uses a buffered sample-and-hold circuit (National Semiconductor LF398) for each of the 9 active patient ECG leads. Logic pulses synchronized to the pacing stimuli are transmitted from the stimulator (Arzco Medical Electronics, Inc.) to the SAS, and trigger the sample-and-hold circuits into the hold mode for 12 ms. Consequently, with the delivery of the pacing stimulus to the patient, the sample-and-hold circuits keep the ECG output voltage constant for the 12-ms blanking period. Patient ECG leads are connected to the appropriate SAS inputs, and the SAS outputs are connected to the corresponding cables of an ECG monitor (Figure 1).

An example of use of the SAS during attempted tachycardia conversion is shown in Figure 2. Review of the records of the 20 patients showed that the SAS

significantly reduced the stimulus artifact. In fact, when unsuppressed artifact did not severely distort the ECG signal and preclude measurement of artifact amplitude, comparison showed that SAS reduced stimulus artifact amplitude to an average of 6.4% (range 1 to 29) of that without SAS.

The occurrence of ECG distortion by stimulus artifact hampers ECG interpretation during transesophageal pacing. Use of the SAS to reduce stimulus artifact amplitude improves the ECG quality. In a newer version of the SAS, the blanking period is variable from 0 to 100 ms rather than being fixed at 12 ms. Thus, it should be possible to reduce the artifact amplitude further and improve the ECG quality even more. Improvement of ECG quality is expected to enhance the diagnostic utility of transesophageal pacing for assessment of ST-segment measurements,4 during tachycardia conversion attempts, or for assessment of atrioventricular conduction and refractory characteristics.

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## Lack of Sustained Hemodynamic Effects of the Beta<sub>2</sub>-Adrenoceptor Agonist Dopexamine in End-Stage Congestive Heart Failure

Michael Böhm, MD, Elisabeth Reuschel-Janetschek, MD, and Erland Erdmann, MD

n congestive heart failure (CHF), a permanent  $\beta$ adrenergic stimulus is imposed on the heart by a compensatory activation of the sympathetic nervous system, which results in increased serum levels of norepinephrine. Since norepinephrine acts primarily on cardiac  $\beta_1$ adrenoceptors, there is a selective down-regulation of  $\beta_1$ adrenoceptors with a preserved  $\beta_2$ -adrenoceptor subpopulation in the myocardium from patients with end-stage CHF.<sup>2,3</sup> These laboratory findings strongly suggest that stimulation of  $\beta_2$  adrenoceptors could provide additional inotropic support to the myocardium in terminal CHF and, hence, might be therapeutically useful in such patients. Dopexamine is a  $\beta_2$ -sympathomimetic compound structurally related to dopamine with no activity on  $\beta_1$ ,  $\alpha_1$ and  $\alpha_2$  adrenoceptors.<sup>4</sup> In a number of clinical trials, dopexamine has been shown to produce beneficial effects in patients with New York Heart Association heart failure, class II to IV.5 Herein, we report the effects of dopexamine on hemodynamics in 4 patients with terminal CHF due to dilated cardiomyopathy before cardiac transplantation.

Four patients (aged 41, 51, 47 and 61 years) with dilated cardiomyopathy were monitored by right-sided heart catheterization in the intensive care unit. All patients had most severe CHF, and were receiving concomitant therapy with dopamine (1.5 to  $2 \mu g/min/kg$  body weight) and dobutamine (10 to  $14 \mu g/min/kg$  body weight) was necessary to maintain blood pressure. None of the patients had to be ventilated. Systolic blood pressure was 90 to 100 mm Hg at entry to the study. The protocol of the study is shown in Figure 1. After a 12-hour

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equilibration period, doses of dopexamine were increased stepwise from 1 to 6  $\mu$ g/min/kg body weight. Hemodynamic measurements were taken immediately before and after a 2-hour infusion period of dopexamine at each dose of the drug. After this, patients were maintained on 6  $\mu$ g/min/kg body weight dosage, and measurements were again taken at 4 to 8 hours during continuation of this dose. The accompanying medication of dopamine and dobutamine was not altered. All patients received digoxin and furosemide. Digoxin serum levels were in the therapeutic range. Two patients were in sinus rhythm and 2 patients had atrial fibrillation. The study protocol was approved by the ethical committee of the University of Munich and was conducted in accordance with the Declaration of Helsinki.

The hemodynamic data are listed in Table I. Dopexamine increased cardiac output at 4 to 6 µg/min/kg body weight. There was a concentration-dependent reduction of mean arterial pressure, whereas systolic blood pressure initially was greatly unchanged. Moreover, there was a slight positive chronotropic response in all patients. The urine output was not significantly altered. After a perfusion duration of 6 to 12 hours at 6 µg/min/ kg body weight, there was hemodynamic deterioration in all patients. Systolic blood pressure was <90 mm Hg in all patients and oliguria occurred in 2. Moreover, there was an increase of the systemic vascular resistance and a decrease in cardiac index. All patients developed clinical evidence of cardiogenic shock and the infusion of dopexamine had to be discontinued. The hemodynamic situation was recompensated during the following days. Since the end of this study, 3 of the 4 patients have been successfully transplanted and 1 patient died 18 days

Our results show that activation of  $\beta_2$  adrenoceptors by dopexamine in patients with terminal CHF produces

FIGURE 1. Study protocol for the infusion of dopexamine (1 to 6  $\mu$ g/min/kg body weight) in patients with terminal congestive heart failure.

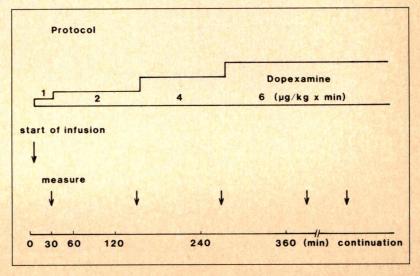


TABLE I Hemodynamic Data of Four Patients with Terminal Heart Failure after Infusion of Dopexamine

		Pre-	1 2			4			6		6× (4 to 6) hours	
	Pt	Drug	Abs	Δ	Abs	Δ	Abs	Δ	Abs	Δ	Abs	
HR	1	81	88	+7	89	+8	87	+6	81	0	115	+34
	2	114	102	-12	109	-5	116	+2	120	+6	127	+13
	3	107	101	-6	116	+9	115	+8	114	+7	108	+1
	4	106	112	+6	109	+3	112	+6	114	+8	118	+12
Mean		102	101	-1.3	106	3.8	108	5.5	107	5.3	117	15
SD		±14.4	±9.8	±9.3	±11.6	±6.4	±13.8	±2.5	±17.7	±3.6	±7.9	±13.8
СО	1	3.2	3.5	+0.3	3.4	+0.2	3.7	+0.5	4.4	+1.2	2.6	-0.6
	2 3	4.2	3.7	-0.5	4.6	+0.4	4.3	+0.1	4.8	-0.6	2.3	-1.9
		3.4	2.9	-0.5	3.5	+0.1	3.1	-0.2	3.4	0	2.4	-1.0
	4	4.1	4.2	+0.1	4.3	+0.2	6.2	+2.1	3.9	-0.2	3.6	-0.5
Mean		3.7	3.6	-0.2	4.0	0.2	4.3	0.6	4.1	0.4	2.7	1.0
SD		±0.5	±0.6	±0.4	±0.6	±0.1	±1.3	±1.0	±0.6	±0.6	±0.6	±0.6
CI	1	1.7	1.8	+0.1	1.8	+0.1	2.0	+0.3	2.3	+0.6	1.4	-0.3
	2	2.2	2.0	-0.2	2.4	+0.2	2.3	+0.1	2.5	+0.3	1.2	-1.0
	2 3	1.8	1.5	-0.3	1.8	+0.1	1.6	-0.1	1.7	-0.0	1.2	-0.5
	4	2.4	2.5	+0.1	2.5	+0.1	3.6	+1.2	2.3	-0.1	2.1	-0.3
Mean		2.0	1.9	-0.1	2.1	0.1	2.4	0.4	2.2	0.2	1.5	-0.5
SD		±0.4	±0.4	±0.2	±0.4	±0.1	±0.9	±0.6	±0.4	±0.3	±0.4	±0.3
PCWP	1	34	34	0	30	+4	30	+4	28	+6	48	+14
	2	26	27	+1	22	-4	23	-3	24	-2	25	-1
	3	23	31	+8	35	+12	33	+10	33	+10	31	+8
	4	28	28	0	32	+4	26	-2	28	0	30	+2
Mean		28	30	2.3	30	4	28	2.3	28	3.5	34	5.8
SD		±4.6	±3.2	±3.9	±5.6	±6.5	±4.4	±6.0	±3.7	±5.5	±10	±6.7

Abs = absolute values; CI = cardiac index (liters/min· $m^2$ ); CO = cardiac output (liters/min); HR = heart rate (beats/min); PCWP = pulmonary capillary wedge pressure (mm Hg); SD = standard deviation; 6X = data taken during (4 to 12 hour) infusion of dopexamine (6  $\mu$ g/min/kg body weight) during decompensation of patients.

an initial increase in cardiac output and a decrease in mean arterial pressure. Besides a cardiotonic effect, it is most likely that these findings at high doses (initially 6  $\mu g/\min/kg$  body weight) could be due to  $\beta_2$  adrenoceptor-mediated vasodilatation resulting in reduction of afterload. Similar findings have been reported in an earlier study<sup>6</sup> in which dopexamine produced hemodynamic improvements at 2 to 6  $\mu g/\min/kg$  body weight. However, in another study,<sup>5</sup> dopexamine was only given for 30 minutes at 6  $\mu g/\min/kg$  body weight, and the patients were in New York Heart Association class II to IV heart failure without concomitant treatment with catecholamines.

The present study suggests that supportive  $\beta_2$  adrenoceptor-mediated positive inotropic effects by dopexamine do not occur in patients with most severe CHF. Hemodynamic deterioration in our patients might have been induced by  $\beta_2$  adrenoceptor-mediated vasodilatation and the CHF of the cardiomyopathic hearts to increase the blood supply to the periphery. These findings are in agreement with in vitro data that show a reduced positive inotropic effect of dopexamine in failing myocardium compared to normal myocardium<sup>3</sup> despite a preserved  $\beta_2$ adrenoceptor subpopulation.<sup>2,3</sup> This phenomenon is most likely explained by an uncoupling of  $\beta_2$  adrenoceptors from the cardiac adenylate cyclase in failing hearts.7 Moreover, a low efficacy of dopexamine in increasing force of contraction, due to partial agonistic properties at the cardiac  $\beta_2$  adrenoceptor, could also play a role.

Other mechanisms also have to be discussed. At high concentrations, dopexamine interacts with  $\beta_1$  adreno-

ceptors of myocardial membranes from the left ventricles of patients with CHF.<sup>2</sup> Hence, an interaction of dopexamine with the positive inotropic effect of dobutamine and dopamine mediated by cardiac  $\beta_1$  adrenoceptors could also occur. Moreover, dopexamine inhibits norepinephrine intake into presynaptic stores.<sup>5</sup> Released norepinephrine could have potentially contributed to the hemodynamic deterioration by increasing afterload in our patients. The clinical consequence of these findings is that in patients with most severe CHF, additional application of dopexamine might lead to hemodynamic deterioration and the therapeutic role of dopexamine is confined to patients with moderate CHF.

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### Leo Schamroth, A Tribute

Giuseppe Oreto, MD

Leo Schamroth died in Johannesburg on May 24, 1988. He was born in Antwerp, Belgium, but he lived in South Africa from the age of 5. He was Professor of Medicine at the University of Witwatersrand, and Chief Physician at Baragwanath Hospital, Johannesburg. Schamroth's name is known to every cardiologist in the world: his books, particularly An Introduction to Electrocardiography and The Disorders of Cardiac Rhythm, have been translated into several languages, and are read everywhere.

To write about Leo Schamroth is to write with both regret and trepidation. The regret is for losing a friend, guide and mentor. The trepidation is for being unable to commemorate and honor him as he deserves. His great presence emanates far beyond the scope of words. Perhaps the best portrayel of Leo Schamroth is contained in the address he delivered at a symposium in honor of Richard Langendorf in 1985, when he described Langendorf as "the epitomy of pure, pristine, logical Aristote-

lian thought."1 Like Richard Langendorf, who died a year earlier, Leo Schamroth represents the most advanced skill in interpreting the surface electrocardiogram. The analytical procedures he used to study the surface electrocardiogram are of great clinical relevance even in an era of highly sophisticated diagnostic procedures. Schamroth's approach to the electrocardiogram was quite similar to the investigative methods of Sherlock Holmes. Leo Schamroth frequently quoted from Sherlock Holmes during his lectures and, indeed, Holmes's sentences are perfectly representative of Schamroth's spirit. The following were written by A. Conan Doyle, but could easily have been written by Leo Schamroth. "It was invisible. I only saw it because I was looking for it." "As a rule the more bizarre a thing is the less mysterious it proves to be." "I have trained myself to see what others overlook." "Never trust upon general impressions, but concentrate

yourself upon details."<sup>2</sup>
The reader of Schamroth's articles and books is fascinated by the simplicity and clarity of his explanations. Nevertheless, if one reads just the title of an article and then looks at the electrocardiograms before reading the text, the diagnosis is often incomprensible. Thereafter, the text reveals that the clue to interpretation is a single detail, just a trifle that initially appeared to be meaningless. Yet with such a clue, the way to the correct diagnosis is clear and immediate.

Leo Schamroth was an excellent teacher. His book, The Disorders of Cardiac Rhythm, is a textbook on arrhythmias read throughout the world. This is because all the topics, even the most complicated, are expressed in an

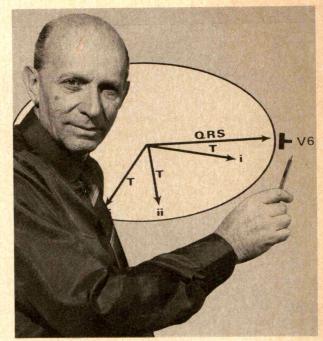


FIGURE 1. Leo Schamroth, MD.

ordinate sequence of sentences where every aspect is clearly explained in detail.

As a lecturer, Leo Schamroth was truly fascinating: he captured his audience not only with his eloquence, but also with an explanation of the electrical phenomena of the heart so clear that the difficult was made easy, and everyone was enriched in listening.

Besides his impressive contribution to electrocardiology as a teacher, Leo Schamroth was also an original thinker and described many new phenomena. In every instance, the approach to the previously unknown truth was based solely on analysis of the surface electrocardiogram. He did not need sophisticated instruments to explore the electrical activity of the heart, nor were his conclusions based on statistical analysis of numerous data. Like Sherlock Holmes, he deduced the truth from simple observations, and logical analysis of the phenomena enabled him to narrow down the possible interpretations until he obtained the solution.

Schamroth's best known innovative idea is that of concealed extrasystoles, namely ectopic impulses that are confined to their ectopic focus, and are therefore inapparent. This was suggested by a patient with intermittent ventricular bigeminy in whom the intervening beats were always in odd numbers.<sup>3</sup> Another important original concept developed by Schamroth is that a semiprotected ventricular focus can be electrotonically influenced by the sinus rhythm. Under certain circumstances, the sinus impulses "force" the ventricular pacemaker to fire, resulting in a ventricular extrasystole. This theory was first reported by Schamroth and Marriott in 1961.<sup>3</sup> In 1976, Jalife and Moe<sup>4</sup> demonstrated, based on laboratory research,

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that a parasystolic pacemaker can be electrotonically influenced (modulated) by the sinus or dominant impulses. Schamroth was delighted by this experimental support to his theory, and became extremely interested in clinical studies on modulated parasystole. Just before his death, he further refined his ideas on the genesis of ventricular extrasystoles, assuming that a ventricular focus behaves like an oscillator. If the oscillator undergoes periodic impulsive perturbations, its response can be mathematically derived by a single simple equation. The curves calculated by Schamroth et al,<sup>5</sup> expressing the entrainment of an oscillator, are almost identical to those characteristic of modulated parasystole, obtained in the laboratory by Jalife and Moe.<sup>4</sup>

The value of Leo Schamroth as a teacher and scientist can be easily deduced from his written works (more than 300 articles, 9 monographs and 11 textbooks). In recognition of his outstanding contributions to the field of electrocardiology, his teaching excellence and his dedicated service, he received innumerable awards, including the Master Teacher Award from the American College of Cardiology, the Grand Orient de Belgique Award, presented only once in 150 years, and the Claude Harris Leon and Percy Fox awards.

But the stature of Leo Schamroth rests on far more than this: his most outstanding characteristic was his greatness as a human being. I cannot try to describe his remarkable qualities for at least 2 reasons. First, I am emotionally involved. It was after meeting Leo Schamroth that I decided to devote myself to electrocardiology. Second, to emphasize the human superiority of Leo Schamroth is somewhat in contrast to his ideas and personality. It is a general rule that the greater a man is, the more simple his behavior. To describe Leo Schamroth from this point of view, it is once again necessary to quote his words about Richard Langendorf, who was described as "the epitomy of unpretentiousness, of unostentatious-

ness, of modesty, of gentleness, of kindness and of humility".1 A further quote is from an article written by one of his co-workers, A. Dubb, on the occasion of Schamroth's retirement: "As head of the department, he has always kept his door open, and any student or staff member, from the most junior to the most senior, could walk in at any time to discuss a problem." Leo Schamroth always kept his door open in the figurative sense as well: he was available for everyone requesting his advice and help. I owe to him the acceptance of several manuscripts for publication, and I am aware that I speak for countless others. He spontaneously offered his help to everyone who either requested it or simply needed it. With his great personality, he enlightened the person who was facing him, but in fact he behaved as if the opposite was occurring: namely he appeared to be the one who was receiving rather than giving, and was grateful for this.

To be in touch with Leo Schamroth was to learn a continuous lesson. He was an outstanding great man in the truest sense of the word, a teacher not only in cardiology but also in life. He will live forever in the memory of everyone who is interested in electrocardiology. Moreover, he will always be present in the hearts of countless people who, like myself, owe him a debt of gratitude.

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### The Complex of Myxomas, Pigmentation and **Endocrine Overactivity**

Wesley S. Bennett, MD, Thomas N. Skelton, MD, and Patrick H. Lehan, MD

arney et all recently described Ca complex consisting of myxomas (cardiac, cutaneous and mammary), pigmentation (cutaneous and mucucutaneous) and endocrine overactivity (Cushing syndrome, sexual precocity and acromegaly). Another such case is described herein.

An 8-year-old girl presented with recent onset exertional dyspnea and lower extremity edema. Birth, growth and development had been unremarkable. Her mother had died at age 26 of complications resulting from a left atrial myxoma. A grade 2/6 holosystolic murmur heard best along the lower left sternal border was audible. Electrocardiogram revealed "P congenitale" with tall peaked P waves in leads I, II and V<sub>1</sub> through V3, and right bundle branch block. Pulmonary pressures at catheterization were within normal limits. The right ventricular cavity was dilated.

She returned at age 12 years with jaundice, right upper quadrant abdominal pain, hepatomegaly and hemolytic anemia. She again underwent right-sided heart catheterization and was found to have a large calcified right atrial mass that at surgery was noted to have completely destroyed the tricuspid valve ("wrecking ball" phenomenon). The myxoma had detached from its connection to the atrial septum. The myxoma and a large portion of the atrial septum were excised, and the tricuspid valve was replaced with a porcine heterograft. She did well until age 24 when she presented with edema, exertional dyspnea and facial features as shown in Figure 1. She had hair on her face, lentigines of the perioral area and facial plethora. Chest x-ray revealed calcific deposits in the cusps of the bioprosthesis in the tricuspid valve position. An echocardiogram revealed evidence of bioprosthetic stenosis and a density in the left atrial cavity. Repeat rightsided heart catheterization revealed a mean tricuspid gradient of 5 mm Hg. Cardiac output was 2.4 liters/ min. The levophase after pulmonary arteriography showed no left-sided heart filling defects. Serum cortisol was elevated and was not lowered with low or high dose dexamethasone therapy, suggesting primary adrenal disease. Computed tomography of the abdomen confirmed bilateral adrenal enlargement. She was treated with oral aminogluthamide and underwent replacement of the bioprosthesis in the tricuspid valve position. At cardiac surgery, she was noted to have a small myxoma of the right atrium. Inspection of the left atrium revealed no tumor. She had bilateral adrenalectomies several months later, and the histology revealed the characteristic pigmented, nodular adrenocortical dysplasia of Carney's complex. Now 6 months after adrenalectomy, she has done well with resolution of the plethora and facial hair.

Carney et al<sup>1</sup> have recently noted the unusual association of 2 very rare disorders, cardiac myxoma and primary pigmented nodular adrenocortical disease. A relatively large proportion of patients were members of the same family suggesting a heritable disorder, most likely inherited in an autosomal dominant fashion.<sup>2</sup> Our patient's mother died at an unusually young age due to cardiac myxoma. She underwent autopsy, and pertinent findings included bilateral "fibrocystic disease" of the breasts. Review by our pathologists confirmed these to be fibroadenomas. Pictures of the patient's mother revealed no abnormal pigmentation.



FIGURE 1. The patient at age 24 year with facial plethora, hirsutism and spotty brown pigmentation of the lips and perioral area.

No evidence of spotty brown pigmentation, endocrine overactivity or abnormality by echocardiogram was noted in 2 maternal aunts evaluated. From telephone interviews with the patient's maternal uncles and maternal grandmother, no history suggesting signs or symptoms related to the complex could be elicited.

Cardiac myxomas that have occurred in members of the same family such as in this case report are exceedingly rare. These familial myxomas have features that differ from sporadic myxomas but are similar to those found in the complex. Familial myxomas occur at a mean age of 26 years compared to 53 years in the sporadic variety. They are also much more likely to be multiple and recurrent compared to sporadic myxomas.3

There are several other associations of cardiac myxoma with abnormal pigmentation but the complex described in our patient and in those patients with Carney's complex is the first to have an associated endocrine abnormality. The myxoid elements of the complex are believed to share the same pathogenic mechanism but characterization of this as neoplastic, hyperplastic or dysplastic is still not determined. In addition, no chromosomal markers have been identified.4

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It is of obvious importance that those patients who have myxomas at a young age (<35 years) should be screened for multiple, recurrent or ventricular myxomas as well as for the associated features of this complex, particularly the endocrine abnormalities. First-degree relatives should likewise undergo evaluation for manifestations of the complex.

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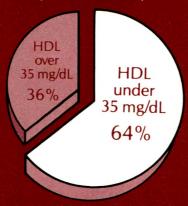


# Solution of the second second

# What's a common denominator of most heart attack victims?

Mixed hyperlipidemias—elevated cholesterol and triglycerides—are common among heart attack victims,<sup>1</sup> and nearly two-thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.<sup>2</sup>

HEART ATTACK PATIENTS (PROCAM TRIAL)<sup>2</sup>



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\*Defined as a combination of definite coronary death and/or definite myocardial infarction.

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Lopid® (Gemfibrozil Capsules and Tablets)

Before prescribing, please see full prescribing information. A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary

Preexisting gallbladder disease (See WARNINGS)

3. Hypersensitivity to gemfibrozil. WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibratetreated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial

was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statisticallysignificantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically

different between Lopid and placebo sub-groups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

 A gallstone prevalence substudy of 450
 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the place bo group, a 55% excess for the gemfibrozil

group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the

group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been

demonstrated and because liver and interstitial cell testicular tumors were increased in Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should

4. Concomitant Anticoagulants — Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If

myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. Initial Therapy — Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every at tempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and

hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** — Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions**—(A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with

tory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage. (B) Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED

4. Carcinogenesis, Mutagenesis, Impairment of Fertility – Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant live neoplasms. In male and female mice, there were no statistically significant differences

Lopid® (Gemfibrozil Capsules and Tablets)

from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell

tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome prolifera-tion following Lopid administration to the male rat. An adequate study to test for peroxtion following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmit-

(gemfibrozil) 600-mg
Tablets

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REDUCES HEART ATTACK

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in

male and female rats, the use of Lopid in pregnancy should be reserved for those pa-tients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. Nursing Mothers — Because of the potential for tumorigenicity shown for gem-fibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. Hematologic Changes — Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months

8. Liver Function - Abnormal liver function tests have been observed occasionally

during Lopid administration, including eleva-tions of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discon tinued. Therefore periodic liver function studies are recommended and Lopid therapy

should be terminated if abnormalities persist.

9. Use in Children – Safety and efficacy in children have not been established. ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study. 2046 patients received Lopid for up to 5 years In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in paren-

theses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant differ-Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%). Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebial hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of musculoskeletal symptoms (See WARNINGS), and to abnormal liver function tests and hematologic changes (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were

more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients. Additional adverse reactions that have been reported for gemfibrozil are listed below

by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:
CAUSAL RELATIONSHIP PROBABLE: Gastrointestinal: cholestatic jaundice; Central

Nervous System: dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; Eye: blurred vision; Genitourinary: impotence; Musculoskeletal: myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS). Clinical Laboratory: increased treatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; Hematopoietic: anemia, leukopenia, bone marrow hypoplasia, eosinophilia; Immunologic: angioedema, laryngeal edema, urticaria; Integumentary: exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: General: weight loss; Cardiac: extrasystoles; Gastrointestinal: pancreatitis, hepatoma, colitis; Central Nervous System: confu-

sion, convulsions, syncope; Eye: retinal edema; Genitourinary: decreased male fertility; Clinical Laboratory: positive antinuclear antibody; Hematopoietic: thrombocytopenia; Immunologic: anaphylaxis, Lupus-like syndrome, vasculitis; Integumentary: alopecia. DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal administered in two divided ooses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with germfibrozii in middle-aged men with dyslipidemia. N Engl J Med

1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.): *The Metabolic Basis of Inherited Disease*, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642. **Caution** – Federal law prohibits dispensing without prescription.

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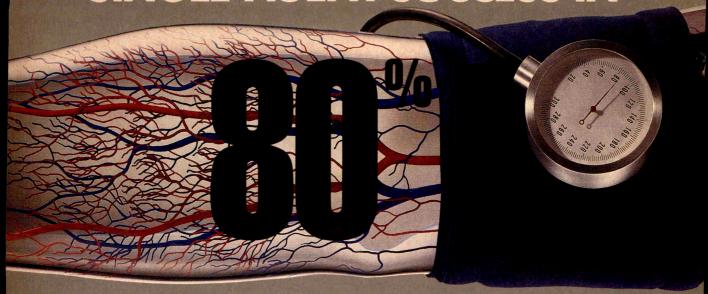
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# American Journal of Cardiology

FEBRUARY 15, 1990, VOL. 65, NO. 7

### **CORONARY ARTERY DISEASE**

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### **Very Early Thrombolytic Therapy in Suspected Acute Myocardial Infarction**

The Thrombolysis Early in Acute Heart Attack Trial Study Group

Three hundred fifty-two patients with suspected acute myocardial infarction were randomized to receive either placebo or tissue-type plasminogen activator, and 29% had treatment initiated before reaching the hospital. Very early thrombolytic therapy can be given without additional risk and can limit the infarct size and improve left ventricular function.

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### The Independence of Cycle Length Variability and **Exercise Testing on Predicting Mortality of Patients Surviving Acute Myocardial Infarction**

Robert E. Kleiger, J. Philip Miller, Ronald J. Krone, J. Thomas Bigger, Jr., and the Multicenter Postinfarction Research Group

We tested the hypothesis that the status of stress test and cycle length variability were measuring the same factor related to mortality. CLV is a measure of autonomic tone, not strongly related to exercise ability, and using the results of both stress testing and CLV allows the identification of subgroups of postinfarction patients with markedly disparate risks of mortality.

### **Ventricular Ectopic Activity During Myocardial Ischemic Episodes in Ambulatory Patients**

Shlomo Stern, Shmuel Banai, Andre Keren, and Dan Tzivoni

Seventy-five consecutive patients with coronary artery disease without known ventricular arrhythmias were studied. In a subgroup of patients in whom Holter monitoring revealed lowgrade ectopic ventricular activity, we observed increased ventricular ectopic activity during ischemic episodes in 31% of these patients and in 27% of their episodes.

### **Usefulness of the Hyperventilation Test in Stable Exertional Angina Pectoris in Selecting Medical**

Diego Ardissino, Paolo Barberis, Stefano De Servi, Colomba Falcone, Maurizio Ferrario, Gloria Demicheli, Paola Zanini, Alberto Rolla, Nicola Bruno, Giuseppe Specchia, and Carlo Montemartini

We studied 83 consecutive patients with stable exertional angina and documented coronary artery disease to evaluate if the detection of abnormal coronary vasoconstriction has therapeutic implications. Hyperventilation induced abnormal coronary vasoconstriction in 16 patients (group I) while 67 (group II) had a negative response. All group I and 16 group II patients underwent repeated hyperventilation and exercise tests after calcium antagonists were given. Results show that hyperventilation testing is able to select patients with stable exertional angina and detectable abnormal coronary vasoconstriction who will improve exercise tolerance with coronary vasodilator treatment.

### Effect of Pretreatment with Aspirin Versus Aspirin Plus Dipyridamole on Frequency and Type of Acute **Complications of Percutaneous Transluminal Coronary Angioplasty**

Nicholas J. Lembo, Alexander J.R. Black, Gary S. Roubin, James R. Wilentz, Larry H. Mufson, John S. Douglas, Jr., and Spencer B. King III

Should dipyridamole be added to aspirin as pretreatment for patients undergoing percutaneous transluminal coronary angioplasty? We prospectively randomized 232 patients to receive either aspirin alone or aspirin plus dipyridamole before elective PTCA. Our results show that the addition of dipyridamole does not significantly reduce acute complications after PTCA, and we now use aspirin alone (325 mg daily) to pretreat patients.

### 427

### **Percutaneous Transluminal Coronary Angioplasty in** the Setting of Large Intracoronary Thrombi

Michael R. Mooney, Jodi Fishman Mooney, Irvin F. Goldenberg, Adrian K. Almquist, and Robert A. Van Tassel

One hundred twelve consecutive patients with extensive coronary thrombi underwent percutaneous transluminal coronary angioplasty and were followed to determine early and late outcomes. In-hospital clinical success was achieved in 92% of patients. At late clinical follow-up, 95% were event free, defined as absence of coronary artery bypass surgery, myocardial infarction or death. These results suggest that PTCA in patients with large intracoronary thrombi may be safer than previously reported.

### **Medical Costs of Coronary Artery Disease in the United States**

Ellison H. Wittels, Joel W. Hay, and Antonio M. Gotto, Jr.

A model was developed to determine the cost of coronary artery disease based on the 5 primary events identified in the Framingham Study: acute myocardial infarction, angina pectoris, unstable angina pectoris, sudden death and nonsudden death; projected costs for angioplasty and coronary bypass surgery were also developed. Our analysis shows that new technologies and new therapies that intervene acutely in patients with CAD have significantly increased the cost for treatment of heart disease.

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### Left Ventricular Hypertrophy Is Associated with Worse Survival Independent of Ventricular Function and Number of Coronary Arteries Severely Narrowed

Richard S. Cooper, Brian E. Simmons, Angel Castaner, Vimala Santhanam, Jalal Ghali, and Maxine Mar

Through the use of a cardiac catheterization registry, we examined whether or not the relation between echocardiographically derived left ventricular hypertrophy and all-cause mortality was independent of LV function and the severity of coronary artery disease. The data demonstrate a consistent pattern of higher death rates during follow-up among patients with LV hypertrophy diagnosed by echocardiography, and this risk was independent of angiographically defined coronary anatomy and systolic ventricular function.

### **ARRHYTHMIAS AND CONDUCTION DISTURBANCES**

### 446

### Spontaneous Sustained Ventricular Tachyarrhythmias During Treatment with Type IA Antiarrhythmic Agents

Peter J. Kudenchuk, Jack Kron, Charles Walance, and John H. McAnulty

Twenty-six patients who developed their first clinical episode of sustained ventricular tachycardia or ventricular fibrillation while taking type IA antiarrhythmic agents for more benign rhythm disturbances were rechallenged with the identical drug during electrophysiologic testing. Patients with drug-associated clinical sustained VT or VF are a heterogenous group who should be evaluated individually and not empirically managed for a proarrhythmic effect by antiarrhythmic drug withdrawal or drug substitution alone.

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### Comparison of Outcome of Paramedic-Witnessed Cardiac Arrest in Patients Younger and Older than 70 Years

Donald D. Tresch, Ranjun K. Thakur, Raymond G. Hoffmann, Tom P. Aufderheide, and Harold L. Brooks

To determine differences in mechanisms of out-of-hospital cardiac arrest between elderly and younger patients, we studied 381 consecutive victims whose arrest was witnessed by paramedics. Patient's age, complaint preceding the arrest and the initial cardiac rhythm associated with the arrest all possessed an independent and significant relation to survival.

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### Changes in Cardiac Output Determined by Continuous-Wave Doppler Echocardiography During Propafenone or Mexiletine Drug Testing

Helmut Lange, Steven Lampert, Martin St. John Sutton, and Bernard Lown

To assess whether continuous-wave Doppler echocardiography can detect changes in foward blood flow due to the negative inotropic effects of antiarrhythmic drugs, we measured peak flow velocity in the ascending aorta, the flow velocity integral (stroke distance), the rate-corrected stroke distance and minute distance (stroke distance × heart rate) during 11 drug trials with mexiletine and 9 drug trials with propafenone. Continuous-wave Doppler echocardiography may be useful to monitor antiarrhythmic drug-induced changes in forward blood flow.

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### Electrophysiologic Determinants of Recurrent Atrial Flutter After Successful Termination by Overdrive

Heinz D. Gössinger, Peter Siostrzonek, Michael Jung, Ludwig Wagner, and Herbert Mösslacher

Is the response to atrial stimulation subsequent to successful atrial flutter termination by overdrive pacing helpful in delineating the risk of recurrence of atrial flutter? We evaluated the ability of electrophysiologic abnormalities to predict recurrence of atrial flutter in 25 patients with stable atrial flutter after restoration of sinus rhythm.

### **SYSTEMIC HYPERTENSION**

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### Antihypertensive Effect of Isradipine Administered Once or Twice Daily on Ambulatory Blood Pressure

Yves Lacourcière, Luc Poirier, Danielle Dion, and Pierre Provencher

Whole-day ambulatory blood pressure monitoring was used to compare the antihypertensive efficacy of isradipine sustained-release once daily with isradipine immediate-release given twice daily in a double-blind randomized crossover study in 76 hypertensive patients. Sustained-release isradipine appears to be effective as a once-daily medication in ambulatory hypertensive patients.

### **VALVULAR HEART DISEASE**

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### Percutaneous Double Balloon Valvotomy for Severe Rheumatic Mitral Stenosis

Carlos E. Ruiz, John W. Allen, and Francis Y.K. Lau

Percutaneous double balloon valvotomy for severe rheumatic mitral stenosis was successfully performed in 281 of 285 consecutive patients. The mean transvalvular gradient decreased from  $16\pm7$  to  $5\pm3$  mm Hg and the cardiac output increased from  $3.8\pm1.0$  to  $5.4\pm1.5$  liters/min, resulting in an increase of the mitral valve area from  $0.86\pm0.24$  to  $2.41\pm0.54$  cm²; symptomatic improvement occurred in 272 of the patients and postdilatation was not significant in the majority of the patients. Therefore, this procedure can be performed at low risk with effective results and a fast recovery.

### CARDIOMYOPATHY

### 479

### Prognostic Significance of Radionuclde-Assessed Diastolic Function in Hypertrophic Cardiomyopathy

Taishiro Chikamori, Shaughan Dickie, Jan D. Poloniecki, Melvyn J. Myers, J. Peter Lavender, and William J. McKenna To evaluate the prognostic significance of diastolic function in hypertrophic cardiomyopathy, we performed technetium-99m gated equilibrium radionuclide angiography in 161 patients. Radionuclide assessment of diastolic function did not improve predictability for 3-year mortality or contribute to the identification of patients at increased risk of sudden death.

### Anti-Beta-Receptor Antibodies in Human Dilated Cardiomyopathy and Correlation with HLA-DR **Antigens**

Constantinos J. Limas, Catherine Limas, Spencer H. Kubo, and Maria-Teresa Olivari

Approximately 30% of patients with idiopathic dilated cardiomyopathy have autoantibodies against the cardiac  $\beta$ -adrenergic receptor. Because the presence of antireceptor antibodies is strongly linked to the HLA-DR4 phenotype, we studied the correlation of HLA-DR antigens in patients with dilated cardiomyopathy, patients with alcoholic cardiomyopathy and normal subjects. Results suggest that the development of anti-βreceptor antibodies in patients with idiopathic dilated cardiomyopathy is under the control of the major histocompatibility

### **CONGENITAL HEART DISEASE**

### **Bradycardia-Mediated Tachyarrhythmias in Congenital Heart Disease and Responses to Chronic Pacing at Physiologic Rates**

Michael J. Silka, James R. Manwill, Jack Kron, and John H. McAnulty

The long-term effects of cardiac pacing on the frequency of various tachyarrhythmias associated with chronic bradycardia were evaluated in 21 young patients with congenital heart disease. Analysis was based on a direct comparison of the number of episodes of the differing tachyarrhythmias during the 12month intervals immediately before and after pacing. Antiarrhythmic drug therapy was not altered during the initial study intervals. Pacing appears to provide an effective therapy for certain achyarrhythmias associated with bradycardia, although critical modes may be necessary.

### **MISCELLANEOUS**

### **Effect of Beta Adrenoceptors and Thyroid Hormones** on Velocity and Acceleration of Peripheral Arterial Flow in Hyperthyroidism

Denis Chemla, Jaime Levenson, Paul Valensi, Yves LeCarpentier, Jean-Claude Pourny, Isabelle Pithois-Merli, and

This study explored the effects of 3 different interventions mechanical exclusion of blood flow to the hand, short-term  $\beta$ blocker treatment and inducement of the euthyroid state—on brachial artery circulation. Ten hyperthyroid patients and 10 normal subjects participated. Results suggest that mean blood velocity relates to peripheral vascular factors, while peak systolic acceleration is related to intrinsic cardiac mechanisms in hyperthyroidism.

### **Cardiac Transplantation in Patients with Preexisting Neoplastic Diseases**

Brooks S. Edwards, Sharon A. Hunt, Michael B. Fowler, Hannah A. Valantine, Edward B. Stinson, and John S. Schroeder

Seven patients with a history of neoplastic disease underwent cardiac transplantation to treat end-stage congestive heart failure. Six of the 7 patients were discharged from the hospital after the transplant and their 1-year survival rate was 71%, compared to 80% for all patients undergoing cardiac transplantation during the same period. This study demonstrates that in carefully selected patients, a history of neoplastic disease need not serve as a contraindication to cardiac transplantation.

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### **Normal Values for Noninvasive Estimation of Left** Ventricular Contractile State and Afterload in Children Rodney C.G. Franklin, Richard K.H. Wyse, Thomas P. Graham, Vanda M. Gooch, and John E. Deanfield

Changing loading conditions make it difficult to assess ventricular contractility in children. Using echocardiography, we studied children with congenital heart disease and our data provide a quantitative basis for assessment of myocardial hy-

pertrophy, afterload and contractile state in childhood.

### **BRIEF REPORTS**

Usefulness of Silent Ischemia, Ventricular Tachycardia, and Complex Ventricular Arrhythmias in Predicting **New Coronary Events in Elderly Patients with Coronary Artery Disease or Systemic Hypertension** Wilbert S. Aronow and Stanley Epstein

### Left Main Coronary Artery Disease Progression After **Percutaneous Transluminal Coronary Angioplasty** Catherine M. Kells, Robert M. Miller, Mark A. Henderson, Judy M. Lomnicki, and Robert G. Macdonald

### **Differential Hemodynamic Effects of Oral Enoximone in Severe Congestive Heart Failure**

Srinivas Murali, Barry F. Uretsky, Anita R. Betschart, Tammy R. Tokarczyk, Judy A. Kolesar, and P. Sudhakar Reddy

**Inotropic Response to Dobutamine in Elderly Patients** with Decompensated Congestive Heart Failure Michael W. Rich and Michael Imburgia

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Long-Term Efficacy and Safety of Coenzyme Q<sub>10</sub> Therapy for Idiopathic Dilated Cardiomyopathy Per H. Langsjoen, Peter H. Langsjoen, and Karl Folkers

### **Prevalence of Significant Congenital Heart Defects in Children of Parents with Fallot's Tetralogy**

Thomas M. Zellers, David J. Driscoll, and Virginia V. Michels

### **Depressed Left Ventricular Systolic Ejection Force in Hypothyroidism**

Richard T. Lee, Maureen Plappert, and Martin G. St. John Sutton

### False-Negative Diagnosis of Proximal Aortic Dissection by Computed Tomography or Angiography and Possible Explanations Based on Transesophageal **Echocardiographic Findings**

Andreas Mügge, Werner G. Daniel, Joachim Laas, Reinhard Grote, and Paul R. Lichtlen

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### **Atrial Standstill After Treadmill Exercise Test and** Unique Response to Isoproterenol Infusion in Recurrent Postexercise Syncope

Yusuke Tamura, Osamu Onodera, Kunio Kodera, Yutaka Igarashi, Takashi Miida, Yoshifusa Aizawa, Tohru Izumi, Akira Shibata, and Satoshi Takano

### FROM THE EDITOR

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### **Limited Research Funds and Cardiac Medicine Without Cardiac Surgery**

William C. Roberts

**INSTRUCTIONS TO AUTHORS on page 538** 

# THE EMERGENCE OF A NEW SOURCE OF 24-HOUR ANTIHYPERTENSIVE AND ANTIANGINAL PROTECTION

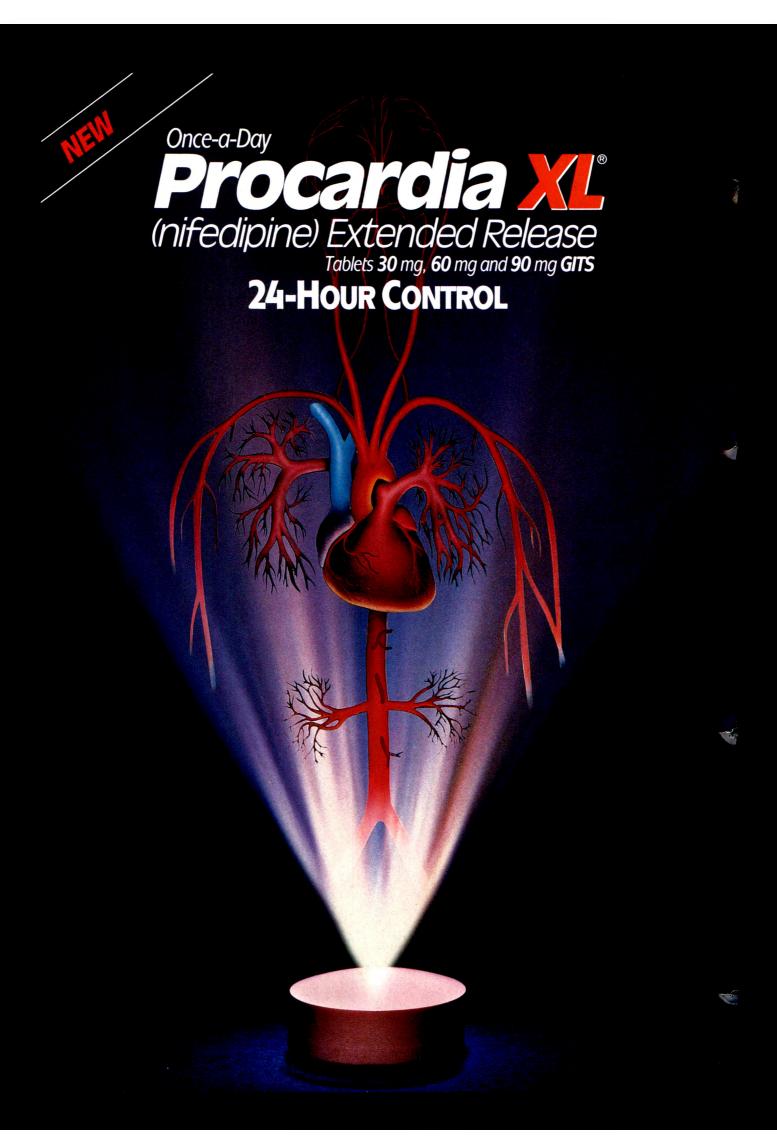
New, Once-a-Day

# Procarcia (nifedipine) Extended Release Tablets 30 mg, 60 mg and 90 mg GITS



© 1989, Pfizer Inc.

Please see brief summary of prescribing information on last page



# FOR <u>BOTH</u> HYPERTENSION AND ANGINA WITH ONCE-DAILY DOSING

### **NOW, Once-Daily Dosing Controls Hypertension**

- The only calcium channel blocker indicated for once-a-day dosing at all doses
- Effective as monotherapy<sup>1</sup> and in combination<sup>2</sup>

### **Once-Daily Dosing Controls Angina**

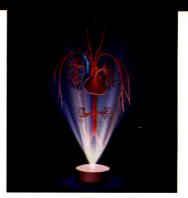
- The only once-a-day calcium channel blocker for angina
- Easy to switch from nifedipine capsules to PROCARDIA XL Extended Release Tablets<sup>3,4</sup>
- PROCARDIA XL angina indications: Patients with proven or suspected vasospastic angina, and patients with classic effort angina who remain symptomatic despite adequate doses of beta blockers and/or nitrates or who cannot tolerate these agents

### **New 24-Hour Controlled-Release Delivery System**

- Releases nifedipine into the gastrointestinal tract at an essentially constant rate over the 24-hour period, independent of pH, with no dose dumping<sup>5,6</sup>
- Minimal serum fluctuations—no significant peaks, no significant troughs<sup>5</sup>
- Low incidence of vasodilatory side effects. The most common side effects are peripheral edema, which is not associated with fluid retention, and headache

In controlled trials of 776 patients with PROCARDIA XL, edema resulted in discontinuation of therapy in 2.7% of patients <sup>4</sup>





### **24-Hour Control for Both Hypertension** AND ANGINA WITH ONCE-DAILY DOSING

### **EASY TO INITIATE ONCE-DAILY DOSING**

 Initiate once-a-day therapy with a single 30-mg or 60-mg PROCARDIA XL Extended Release Tablet, swallowed whole

### **EASY TO SWITCH TO ONCE-DAILY DOSING**

• Over 90% of angina patients controlled on nifedipine capsules were easily switched and controlled on PROCARDIA XL Extended Release Tablets at the nearest equivalent total daily dose; others needed dosage adjustment4

### TITRATION SHOULD PROCEED AS CLINICALLY WARRANTED

For full dosage instructions, see prescribing information

References: 1. Gavras I. Mulinari R. Gavras H. et al: Antihypertensive effectiveness of the nifedipine gastrointestinal therapeutic system. Am J Med 1987;83(suppl 6B):20-23. 2. Frishman WH, Garofalo JL. Rothschild A: The nifedipine gastrointestinal therapeutic system in the treatment of hypertension. Am J Cardiol 1989;64(suppl to No. 11):65F-69F. 3. Vetrovec GW. Parker VE. Cole S, et al: Nifedipine gastrointestinal therapeutic system in stable angina pectoris: Results of a multicenter open-label crossover comparison with standard nifedipine. Am J Med 1987;83(suppl 6B):24-29. 4. Data on file. Medical Department. Pfizer Laboratories, Pfizer Inc, New York. 5. Chung M, Reitberg DP, Gaffney M, et al: Clinical pharmacokinetics of nifedipine gastrointestinal therapeutic system: A controlled-release formulation of nifedipine. Am J Med 1987;83(suppl 6B):10-14. 6. Swanson DR, Barclay BL, Wong PSL, et al: Nifedipine gastrointestinal therapeutic system. Am J Med 1987;83(suppl 6B):3-9.

Brief Summary
PROCARDIAX (\* (nifedipine) Extended Release Tablets
For Oral Use
CONTRAINDICATIONS: Known hypersensitivity reaction to nifedipine
WARNINGS: Excessive Hypotension. Although in most angina patients the hypotensive effect of nifedipine is modest and well tolerated,
working the time of subsequent upward dosage adjustment, and may be not responses have usually occurred during initial thration
or at the time of subsequent upward dosage adjustment, and may be not reported in patients receiving nitedlipine together with a
best-blocking agent who underwent cornonary after typass surgery using high dose lentarialy ansethesia. The interaction with high dose
fentaryl appears to be due to the combination of nifedipine and a beta blocker, but the possibility that it may occur with nifedipine alone,
with low doses of fentaryl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In integline treated
patients where surgery using high dose fentaryl anesthesia is contemplated, the physician should be aware of these potential problems
and if the patients condition permits, sufficient time at least 50 hours; should be allowed for intelligente to be washed out of the body prior
to surgery.

pine. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased enterity to catecholomies. Initiation of infecipine treatment will not prevent this occurrence and on occasion has been reported to increase!

Congactive Hard Britise Rarely, patients usually receiving a beta blocker, have developed heart failure after beginning nifedipries. Congactive Hard Britise Rarely, patients usually receiving a beta blocker, have developed heart failure after beginning nifedipries. Petases benefit to those patients usually received to be of less benefit to those patients, using the time of the patients are sent to the sent and the patients are sent and the sent and the patients are sent and the sent and the patients are sent a

thought to be a function of inhibition of calcium transport across the platetet memorane, no crimical significance in unsee minungs misseen demonstrativy of this laboratory test, including hemolysis, could not be determined. Positive direct Combis test with without hemolysis could not be determined exported to exert a beneficial effect in certain cases, are reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to in indeptine theretary is uncertain in most cases but proposible in some. During Interactions—Beta-addrenergic blocking agents; (See WARNINGS) Experience in over 1400 patients with procardia\* capsules in a noncomparative inclinact that has shown that concomnation of infections ento deta-blocking agents is susually well beta-add but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angline.

Severe hypotension, or exacerbation of angline.

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Long Acting Nitrates. Nidedpine may be safely co-administered with nitrates, but there nave been no controlled situation and interest the combination.

Digitalis: Administration of nifedipine with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigant round no increase in digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigant round no increase in digoxin levels may be the control of the

Carcinogenesis, Mulagenesis, Impairment of Fertility: Nifedipine was administered orally to rats, for two years and was not shown to carcinogenic. When given to rats prior to mating, infedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. In vivor mulagenicity studies were negative. Prepanary: Prepanar

tinnitis. "Iraquential reproductive" breast pain, dysuria, hematuria, nocturia.

Alverse experiences winch courred in less than 1 in 1000 patients cannot be distinguished from concurrent disease states or medications.

Alverse experiences winch courred in less than 1 in 1000 patients cannot be distinguished from concurrent disease states or medications.

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# Introducing The New Q-cath R/M

### uinton's New Front-End ecording and Monitoring stem for Cath Labs

he Q-cath R/M Recording and Ionitoring System is Quinton's answer numerous requests for a more basic ersion of our popular Q-cath System.

ot every cath lab needs the omputerized analysis and data storage apabilities of Q-cath. But many want benefits of its leading-edge echnology. And Q-cath R/M delivers tose benefits.

### ouch-Screen Controls Simplify peration

he touch screen puts all system ontrols at your fingertips and implifies operation by presenting only nose functions needed at the moment. Ising the touch screen, you can uickly calibrate transducers, format

the waveform display and recorder printouts, and enter patient data.

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You can distinguish between waveforms at a glance because the color monitor displays each ECG and pressure waveform in a different color. The all-digital monitor is highly reliable and easy on the eyes.

### Chart Recorder Saves Money

The Q-cath R/M chart recorder produces sharp images on non-silver paper—providing cost savings of up to 80% over expensive silver paper. The pre-folded perforated paper stacks neatly as it is printed, saving technician time by eliminating the need to fold and cut it after the procedure.

### New Approach to Signal Conditioning Improves Signal Quality

Digital signal transmission minimizes baseline drift, improves signal fidelity and simplifies transducer calibration. One compact multi-channel signal-conditioning module replaces the racks of modules used in most conventional cath lab systems.

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CONTENTS/ABSTRACTS

# American Journal

FEBRUARY 15, 1990, VOL. 65, NO. 7

### **CORONARY ARTERY DISEASE**

### Very Early Thrombolytic Therapy in Suspected Acute **Myocardial Infarction**

The Thrombolysis Early in Acute Heart Attack Trial Study Group

We randomized 352 patients with suspected acute myocardial infarction (AMI) to placebo (175) or tissue-type plasminogen activator (rt-PA) (177). Patients <75 years of age were eligible if evaluated within 165 minutes from onset of chest pain. In 29% of the patients treatment was initiated outside of the hospital. AMI was diagnosed in 59% of all randomized patients. The incidence was similar in the 2 groups (placebo, 108, rt-PA, 101). Among rt-PA-treated patients there were significantly fewer Qwave infarctions and rt-PA was associated with significantly decreased infarct size (serum lactate dehydrogenase isoenzyme<sub>1</sub> activity) and an increased ejection fraction (radioangiography). Benefit was restricted to patients with ST-segment elevation on the initial electrocardiogram. There were 18 (10.3%) and 11 (6.2%) deaths (p = 0.23) within 30 days in the placebo and rt-PA groups. Adverse reactions were similar in both groups with no excess of complications in the home-treated group.

### The Independence of Cycle Length Variability and Exercise **Testing on Predicting Mortality of Patients Surviving Acute Myocardial Infarction**

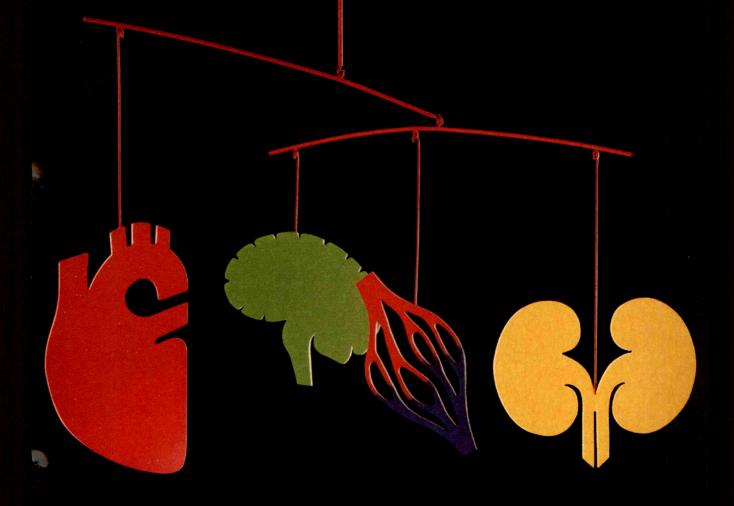
Robert E. Kleiger, J. Philip Miller, Ronald J. Krone, J. Thomas Bigger, Jr., and the Multicenter Postinfarction Research Group

Cycle length variability (CLV), defined as the standard deviation of normal cycle length intervals, has been found to be a powerful predictor of subsequent mortality in survivors of acute myocardial infarction. Decreased CLV is associated with a significant increase in mortality. We tested the hypothesis that the status of stress test and CLV were measuring the same factor related to mortality. Although the distribution of CLV was shifted to higher CLV in patients who completed the test and to lower CLV in those who failed to take the test, both predictors of mortality remained independent predictors of long-term mortality (average of 31 months of follow-up) after controlling for each other. Moreover, subgroups with an approximate 15-fold difference in mortality were defined using both variables. CLV is a measure of autonomic tone, not strongly related to exercise ability, and using the results of both stress testing and CLV results in the identification of subgroups of postinfarction patients with markedly disparate risks of mortality.



*In hypertension, in heart failure\** 

# A BALANCE OF BENEFITS FOR YOUR OLDER CV PATIENTS



- Promotes LVH regression¹
- Tends to sustain cerebral blood flow<sup>2</sup>
- Does not adversely affect lipid profile<sup>3</sup>
- Tends to sustain renal blood flow<sup>4</sup>

Your therapeutic choice today,



can offer patients a lifetime of benefits.

\*CAPOTEN is indicated for the treatments of both hypertension and heart failure. CAPOTEN may be used as initial therapy only for hypertensive patients with normal renal function in whom the risk of neutropenia/ agranulocytosis is relatively low (I out of over 8,600 in clinical trials). CAPOTEN also may be used in patients with heart failure who have not responded adequately to treatment with diuretics and digitalis. Although the beneficial effect of captopril in heart failure does not require the presence of digitalis, most controlled clinical trial experience with captopril has been in patients receiving digitalis, as well as diuretic treatment. Consequently, CAPOTEN should generally be added to both of

these agents except when digitalis use is poorly tolerated or otherwise not feasible. In using CAPOTEN, consideration should be given to the risk of neutropenia/agranulocytosis. Use special precautions in all patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white blood cells or immune response. Evaluation of hypertensive and heart failure patients should always include assessment of renal function. See INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.



### **TAPOTEN®** Your therapeutic choice today can mean a lifetime of patient benefits (captopril tablets)

References: 1. 1988 Joint National Committee: The 1988 report of the Joint National Committee on detection, evaluation, and treatment of high blood pressure. Arch Intern Med 148:1023-1038, 1988. 2. Raulson OB, Waldemar G, Andersen AR, et al: Role of angiotensin in autoregulation of cerebral blood flow. Circulation 77 (suppl I):1-55—1-58, 1988. 3. Weinberger MH: Anti-hypertensive therapy and lipids: Evidence, mechanisms, and implications. Arch Intern Med 145:1102-1105, 1985. 4. Duchin KL, Willard DA: The effect of captopril on renal hemodynamics in hypertensive patients. J Clin Pharmacol 24:351-359, 1984. ive patients. J Clin Pharmacol 24:351-359, 1984.

### CAPOTEN® TABLETS

INDICATIONS: Hypertension—CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/ agranulocytosis (see WARNtension. Consideration should be given to the risk of neutropenia/ agranulocytosis (see warns INGS). CAPOTEN is effective alone and in combination with other antihypertensive agents specially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in the treatment of congestive heart failure in patients who have not responded adequately to treatment with diuretics and digitalis. CAPOTEN should generally be added to both of these agents except when digitalis use is poorly tolerated or otherwise not feasible

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product.

WARNINGS: Angioedema—Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been seen in patients treated with ACE inhibitors, including captopril. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Emergency therapy, including but not necessarily limited to, subcutaneous administration of a 1:1000 solution of epinephrine should be promptly instituted.

Neutropenia/Agranulocytosis-Neutropenia (<1000/ mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular diseases, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their distribution of the relative of their distribution of the relative systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. Evaluation of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is esuspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins >1 g per day were seen in about 0.7% of patients on captopril.

Proteinuria: Total urinary proteins >1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses >150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salf/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]). In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients brould be followed closely for the first 2 weeks for freatment and whenever the dose of canton ill. should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: Impaired Renal Function-Hypertension-Some hypertensive pa-PRECAUTIONS: General: Impaired Renal Function—Hypertension—Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe prexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS (Altered Laboratory Findings). Valvular Stenosis—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. Surgery/Anesthesia—If hypotension, occurs during surgery or anesthesia, and is considered due to the efthesia—If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: Hypotension—Patients on Diuretic Therapy—Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasadilator Activity—In heart failure patients, vasadilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution. Agents Increasing Serum Potassium—Give potassium—sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution. Inhibitors of Endogenous Prostaglandin Synthesis—Indomethacin and other nonsteiroidal antifilammatory agents may reduce the antihyportensive effect of captopril, especially in low

inflammatory agents may reduce the antihypertensive effect of captopril, especially in low

renin hypertension.

Lithium—Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C: Embryocidal effects and craniofacial malformations were observed in rabbits. Human Experience—There are no adequate and well-controlled studies of captopril in

in rabbits. Human Experience—There are no adequate and well-controlled studies of captopril in pregnant women. Data are available that show captopril crosses the human placenta. Captopril should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Based on post-marketing experience with all ACE inhibitors, the following information has been collected. Inadvertent exposure limited to the first trimester of pregnancy does not appear to affect fetal outcome adversely. Fetal exposure during the second and third trimester of pregnancy has been associated with fetal and neonatal morbidity and mortality. When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported. Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors but it is not clear whether they are related to ACE inhibition, maternal hypertension or the underlying prematurity. There is no experience with exchange transfusion, hemodialysis or peritoneal dialysis for

removing captopril from the neonatal circulation.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approxi-

Renal—About 1 of 100 patients developed proteinuria (see WARNINGS), Renal insufficiency,

renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

thrombocytopenia, and pancytopenia have been reported.

Dermatologic—Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest care and explicit there exert in a hourt of 100 patients.

Interactions for discussion of hypotension of influence of captopri therapy, lacrycardia, charge pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients. 

Dysgeusia—Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months).

Angioedema—Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been reported in approximately one in 1000 patients. Angioedema involving the upper airways has caused fatal airway obstruction. (See WARNINGS.)

The following have been reported in about 0.5 to 2 percent of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials: gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcray. peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alo-

Other clinical adverse effects reported since the drug was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined.

General: Asthenia, gynecomastia.

Cardiovascular: Cardiac arrest, cerebrovascular accident, syncope

Dermatologic: Bullous pemphigus.
Gastrointestinal: Pancreatitis, glossitis.
Hematologic: Anemia, including aplastic and hemolytic.
Hepatobiliary: Hepatitis, including rare cases of necrosis, cholestasis.
Metabolic: Symptomatic hyponatremia.

Metadoric, Symptomatic Hina.
Musculoskeletal: Myagia, myasthenia.
Nervous/Psychiatric: Ataxia, confusion, depression, nervousness, somnolence.
Respiratory: Bronchospasm, eosinophilic pneumonitis, rhinitis.
Special Senses: Blurred vision.

As with other ACE inhibitors, a syndrome has been reported which includes: fever, myalgia arthralgia, rash or other dermatologic manifestations, eosinophilia and an elevated ESR. Findings have usually resolved with discontinuation of treatment.

Altered Laboratory Findings: Serum Electrolytes: Hyperkalemia: small increases in serum potassium, especially in patients with renal impairment (see PRECAUTIONS). Hyponatremia: particularly in patients receiving a low sodium diet or concomitant diuretics. BUN/Serum Creatinine: Transient elevations of BUN or serum creatinine especially in volume or salt depleted patients or those with renovascular hypertension may occur. Rapid reduction of longstanding or markedly elevated blood pressure can result in decreases in the glomerular filtration rate and, in turn, lead to increases in BUN or serum creatinine.

Hematologic: A positive ANA has been reported.

Liver Function Tests: Elevations of liver transaminases, alkaline phosphatase, and serum

bilirubin have occurred.

**OVERDOSAGE:** Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by vs. dosage adjustments are recommended for patients with impaired renal function. Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, and 50 mg in bottles of 100 and 1000; 100 mg in bottles of 100; and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658R)

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#### **Ventricular Ectopic Activity During Myocardial Ischemic Episodes in Ambulatory Patients**

Shlomo Stern, Shmuel Banai, Andre Keren, and Dan Tzivoni

Seventy-five consecutive patients with coronary artery disease without known ventricular arrhythmias were studied. Holter monitoring revealed increased ventricular ectopic activity during ischemic episodes in 15% of the patients, and in 6% of the episodes, but no malignant arrhythmias were detected. In a subgroup of patients in whom Holter revealed low-grade ectopic ventricular activity (ventricular premature contractions ≥14/24 hours), increased ventricular ectopic activity during ischemic episodes was observed in 31% of these patients and in 27% of their episodes.

#### Usefulness of the Hyperventilation Test in Stable Exertional **Angina Pectoris in Selecting Medical Therapy**

Diego Ardissino, Paolo Barberis, Stefano De Servi, Colomba Falcone, Maurizio Ferrario, Gloria Demicheli, Paola Zanini, Alberto Rolla, Nicola Bruno, Giuseppe Specchia, and Carlo Montemartini

To evaluate whether the detection of abnormal coronary vasoconstriction in stable exertional angina may have therapeutic implications, we studied 83 consecutive patients with stable exertional angina and documented coronary artery disease. Abnormal coronary vasoconstriction was induced by hyperventilation in 16 patients (group I) while 67 had a negative response (group II). All group I patients and 16 group II patients repeated hyperventilation and exercise tests after the administration of dihydropyridine calcium antagonist drugs. After treatment 15 of 16 patients in group I had a negative response to the hyperventilation test, and the total exercise duration significantly increased (278  $\pm$  183 vs 554  $\pm$  248 seconds, p < 0.001). No differences were observed between pre- and posttreatment values in group II patients. These data show that the hyperventilation test is able to select a subset of patients with stable exertional angina and detectable abnormal coronary vasoconstriction who improve their exercise tolerance by coronary vasodilator treatment.

#### **Effect of Pretreatment with Aspirin Versus Aspirin Plus** Dipyridamole on Frequency and Type of Acute Complications of Percutaneous Transluminal Coronary Angioplasty

Nicholas J. Lembo, Alexander J.R. Black, Gary S. Roubin, James R. Wilentz, Larry H. Mufson, John S. Douglas, Jr., and Spencer B. King III

We prospectively randomized 232 patients to receive aspirin 325 mg orally 3 times daily (group 1, n = 115) or aspirin 325 mg orally 3 times daily plus dipyridamole 75 mg orally 3 times daily (group 2, n = 117) before elective percutaneous transluminal coronary angioplasty (PTCA). All clinical, angiographic and PTCA-related variables were similar between groups.

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The angiographic success rate was 93% in both groups. Clinical success was achieved in 107 patients (92%) in group 1 and in 101 patients (88%) in group 2 (difference not significant). Q-wave myocardial infarction occurred in 2 patients (1.7%) in group 1 and 5 patients (4.3%) in group 2 (difference not significant). Emergency coronary artery bypass grafting was required in 3 patients (2.6%) in group 1 and 7 patients (6.1%) in group 2 (difference not significant). There was 1 in-hospital death (group 2). The addition of dipyridamole to aspirin as pretreatment of patients undergoing PTCA did not significantly reduce acute complications compared to aspirin alone.

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#### **Percutaneous Transluminal Coronary Angioplasty in the Setting of Large Intracoronary Thrombi**

Michael R. Mooney, Jodi Fishman Mooney, Irvin F. Goldenberg, Adrian K. Almquist, and Robert A. Van Tassel

One hundred twelve consecutive patients with angiographically defined extensive coronary thrombi were treated with coronary angioplasty and followed prospectively to determine early and late outcomes. Clinical success was achieved in 103 patients (92%) at hospital discharge. Elective coronary artery bypass surgery was required in 4 patients (3.5%), and 4 patients (3.5%) required emergency coronary artery bypass grafting because of abrupt closure. At late clinical follow-up, 95% had event-free follow-up defined as absence of coronary artery bypass surgery, myocardial infarction or death. In conclusion, coronary angioplasty alone—without concomitant thrombolytic therapy or prolonged heparin pretreatment may allow for a good early and late outcome.

#### **Medical Costs of Coronary Artery Disease in the United States** Ellison H. Wittels, Joel W. Hay, and Antonio M. Gotto, Jr.

The cost of coronary artery disease (CAD) is high and increasing. A model has been developed to determine the cost of CAD based on the 5 primary events identified in the Framingham Study: acute myocardial infarction, angina pectoris, unstable angina pectoris, sudden death and nonsudden death. In addition, projected costs for angioplasty and coronary bypass surgery have been developed. The cost estimates were for a 5year period and were based on published findings for the frequency and expected outcome of events and procedures, a consultant panel of cardiologists from across the country and prevailing prices in 1986 US dollars. The estimated 5-year costs ranged between \$9,078 for sudden death to \$51,211 for acute myocardial infarction. This model offers a better understanding of the costs for the care of patients with CAD. At this time there is no effective model that does this. The high cost of CAD reflects the improved technology and more effective and expensive therapies now available. Newer therapies have significantly increased the cost for treatment of heart disease.

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- No reported episodes of infusion-related hypotension requiring emergency intervention

Bleeding is the most common complication of thrombolytic therapy, with intracranial bleeding being the most serious. Activase® is contraindicated in patients with: active internal bleeding, history of cerebrovascular accident, recent (within two months) intracranial or intraspinal surgery or trauma, intracranial neoplasm, arteriovenous malformation, or aneurysm, known bleeding diathesis, severe uncontrolled hypertension. (See WARNINGS section of brief summary of prescribing information.)

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Please see brief summary of prescribing information on facing page.

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Brief Summary
Consult full prescribing information before using.

Consult full prescribing information before using.

INDICATIONS AND USAGE: ACTIVASE® is indicated for use in the management of acute myocardial infarction (AMI) in adults for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms.

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, ACTIVASE® is contraindicated in the following situations: - Active internal bleeding - History of creatpovascular accident - Recent (within two months) intracranial or intraspinal surgery or trauma (see WARNINGS) - Intracranial neoplasm, arteriovenous malformation, or aneurysm - Known bleeding diathesis - Severe uncontrolled hypertension.

is contraindicated in the following situations: Active internal bieeding - History of cerebrovascular accident - Recent (within two months) intracranial or intraspinal surgery or trauma (see WARNINGS) - Intracranial neoplasm, arteriovenous malformation, or aneurysm - Known bleeding diathesis - Severe uncontrolled hypertension.

WARNINGS: Bleeding The most common complication encountered during ACTIVASE\* therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: - Internal bleeding involving the gastrointestinal or genitourinary tract, or retropertioneal or intracranial sites - Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutidown, arterial puncture, recent surgical intervention).

Concomitant use of heparin anticoagulation may contribute to bleeding. Some hemorrhagic episodes occurred one or more days after the effects of ACTIVASE\* had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during ACTIVASE\* therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including sites of catheter insertion, arterial and venous puncture, cutdown and needle puncture).

Intramuscular injections and nonessential handling of the patient should be avoided during treatment with ACTIVASE\* Venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of ACTIVASE\* it is preferable to use an upper extremity vessel accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding. Should serious bleeding (not controllable by local pressure) occur, the infusion of ACTIVASE\* and any concomitant heparin should be terminated immediately.

Each patient being considered for therapy with ACTIVASE\* should be carefully evaluated and antic

extent mitigate this phenomenon.

Drug Interactions The interaction of ACTIVASE® with other cardioactive drugs has not been studied. In

Drug Interactions The interaction of ACTIVASE® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platef function may increase the risk of bleeding if administered prior to, during or after ACTIVASE® therapy. Use of Anticoagulants Heparin has been administered concomitantly with and following infusions of ACTIVASE® to reduce the risk of rethrombosis. Because either heparin or ACTIVASE® alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites. Pregnancy (Category C) Animal reproduction studies have not been conducted with ACTIVASE® It is also not known whether ACTIVASE® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ACTIVASE® should be given to a pregnant woman only if clearly needed

clearly needed.

Pediatric Use Safety and effectiveness of ACTIVASE® in children has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which evaluated tumorigenicity of ACTIVASE® and effect on tumor metastases in rodents, were negative. Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure and only at the highest concentrations tested.

Nursing Mothers It is not known whether ACTIVASE® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ACTIVASE® is administered to a

ADVERSE REACTIONS: Bleeding The most frequent adverse reaction associated with ACTIVASE® is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

The following incidence of significant internal bleeding (estimated as >250 cc blood loss) has been reported in studies in over 800 patients treated at all doses:

Total Dose ≤ 100 mg Total Dose > 100 mg

gastrointestinal	5%	5%
genitourinary	4%	4%
ecchymosis	1%	<1%
retroperitoneal	<1%	<1%
epistaxis	<1%	<1%
gingival	<1%	<1%

The incidence of intracranial bleeding in patients treated with ACTIVASE® Alteplase, recombinant, is as follows:

Dose	Number of Patients	<u>%</u>
100 mg	3272	0.4
150 mg	1779	1.3
1-1.4 mg/kg	237	0.4

These data indicate that a dose of 150 mg of ACTIVASE® should not be used because it has been associated with an increase in intracranial bleeding.

Recent data indicate that the incidence of stroke in 6 randomized double-blind placebo controlled trials17 is not significantly different in the ACTIVASE® treated patients compared to those treated with placebo (37/3161, 1.2% versus 27/3092, 0.9%, respectively) (p = 0.26).

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur. ACTIVASE® therapy should be discontinued immediately, along with any concomitant therapy with heparin.

Fibrin, which is part of the hemostatic plus formed at needle produce sites will be used.

therapy with heparin.

Fibrin, which is part of the hemostatic plug formed at needle puncture sites, will be lysed during ACTIVASE\* therapy. Therefore, ACTIVASE\* therapy requires careful attention to potential bleeding sites. 
Allergic Reactions No serious or life-threatening allergic reactions have been reported. Other mild hypersensitivity reactions such as urticaria have been observed occasionally.

Other Adverse Reactions Other adverse reactions have been reported, principally nausea and/or vomiting, hypotension, and fever. These reactions are frequent sequelae of MI and may or may not be attributable to ACTIVASE\* therapy.

DOSAGE AND ADMINISTRATION: Administer ACTIVASE® as soon as possible after the onset

of symptoms.

ACTIVASE® is for intravenous administration only.

The recommended dose is 100 mg administered as 60 mg (34.8 million IU) in the first hour (of which 6 to 10 mg is administered as a bolus over the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 mg (11.6 million IU) over the third hour. For smaller patients (less than 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.8

A DOSE OF 150 MG OF ACTIVASE® SHOULD NOT BE USED BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Although the use of anticoagulants and antiplatelet drugs during and following administration of ACTIVASE® has not been shown to be of unequivocal benefit, heparin has been administered concomitantly for 24 hours or longer in more than 90% of patients. Aspirin and/or dipyridamole have been given either during and/or following heparin treatment.

Reconstitution and Dilution DO NOT USE IF VACUUM IS NOT PRESENT.

ACTINASE\* should be reconstituted by aseptically adding the appropriate volume of the accompanying Sterile Water for Injection, USP to the vial. It is important that ACTINASE\* be reconstituted only with
Sterile Water for Injection, USP without preservatives. Do not use Bacteriostatic Water for Injection
USP The reconstituted preparation results in a colorless to pale yellow transparent solution containing
ACTINASE\* 1.0 mg/mL at approximately pH 7.3. The osmolality of this solution is approximately

251 mOsm/kg.

Because ACTIVASE\* contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution may be used for intravenous administration within 8 hours following recording tution when stored between 2-30°C. Before further dilution or administration, the product should be visually inspected for particulate matter and discoloration prior to administration whenever solution and

container permit.

ACTIVASE® is stable for up to 8 hours in these solutions at room temperature. Exposure to light has o effect on the stability of these solutions. Excessive agitation during dilution should be avoided, nixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion olutions, e.g., Sterile Water for Injection, USP or preservative-containing solutions for further dilution.

No other medication should be added to infusion solutions containing ACTIVASE. Any unused

infusion solution should be discarded.

HOW SUPPLIED: ACTIVASE\* is supplied as a sterile, lyophilized powder in 20 mg and 50 mg vials containing vacuum, each packaged with diluent for reconstitution.

Storage Store lyophilized ACTIVASE\* at controlled room temperature not to exceed 30°C (86°F), or under refrigeration (2-8°C/36-46°F). Protect the lyophilized material during extended storage from processing processors.

excessive exposure to light. Do not use beyond the expiration date stamped on the vial. ACTIVASE®, Alteplase, recombinant Manufactured by

GENENTECH®, INC.

South San Francisco, CA 94080

REFERENCES:
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#### Left Ventricular Hypertrophy Is Associated with Worse Survival Independent of Ventricular Function and Number of **Coronary Arteries Severely Narrowed**

Richard S. Cooper, Brian E. Simmons, Angel Castaner, Vimala Santhanam, Jalal Ghali, and Maxine Mar

Left ventricular (LV) hypertrophy is a well-defined secondary cardiovascular risk factor. Insufficient data exist at the present time, however, to estimate the true independence of this relation because persons with longstanding hypertension are at high risk for both LV hypertrophy and other hypertension-related sequelae. Through the use of a cardiac catheterization registry we examined whether or not the relation between echocardiographically derived LV hypertrophy and all-cause mortality was independent of LV function and the severity of coronary artery disease. Among 744 patients with echocardiographic LV mass determinations, a significantly larger left ventricle was found among decedents compared to survivors (131  $\pm$  47 vs 116  $\pm$  38 g/m, p = 0.014). In Cox regression analysis this relation was independent of the number of stenotic coronary vessels and ejection fraction (p <0.01). Thickness of the posterior wall and ventricular septum had even greater independent predictive power than did the global estimate of LV mass.

#### ARRHYTHMIAS AND CONDUCTION DISTURBANCES

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#### **Spontaneous Sustained Ventricular Tachyarrhythmias During** Treatment with Type IA Antiarrhythmic Agents

Peter J. Kudenchuk, Jack Kron, Charles Walance, and John H. McAnulty

Twenty-six patients who developed their first clinical episode of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) while taking type IA antiarrhythmic agents for more benign rhythm disturbances were rechallenged with the identical drug during electrophysiologic testing. Sustained VT or VF was induced in 65% of these patients while drug-free and in 58% of patients after receipt of their previously taken antiarrhythmic drug. Most patients with inducible or noninducible sustained VT or VF while drug-free had a concordant result when rechallenged with the drug associated with their clinical arrhythmia. Continued use of an antiarrhythmic agent different from that being administered when their clinical VT or VF occurred was frequently associated with recurrent spontaneous VT or VF during follow-up. Patients with drug-associated clinical sustained VT or VF are a heterogenous group who should be evaluated individually and not empirically managed for a "proarrhythmic" effect by antiarrhythmic drug withdrawal or drug substitution alone.

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†Patent pending.

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#### Comparison of Outcome of Paramedic-Witnessed Cardiac **Arrest in Patients Younger and Older than 70 Years**

Donald D. Tresch, Ranjun K. Thakur, Raymond G. Hoffmann, Tom P. Aufderheide, and Harold L. Brooks

To determine differences in mechanisms of out-of-hospital cardiac arrest between elderly and younger patients, we studied 381 consecutive victims whose arrest was witnessed by paramedics; the arrest occurred in the presence of paramedics and in 91% of patients the cardiac rhythm was monitored at the time of the arrest. Patients were divided into 2 age groups: elderly patients were >70 years (187) and younger patients were <70 years (194). Elderly patients could be as successfully resuscitated and hospitalized as younger patients; however, 24% of younger patients survived, compared to only 10% of elderly patients. Before arrest elderly patients more commonly complained of dyspnea (53 vs 40%, p <0.009), whereas younger patients more commonly had chest pain (27 vs 13%, p <0.001). Initial cardiac rhythm associated with the arrest varied according to the patient's age and the patient's complaint preceding the arrest. Ventricular fibrillation occurred in 42% of younger patients, compared to 22% of elderly patients. Sixty-eight percent of patients with chest pain demonstrated ventricular fibrillation, whereas ventricular fibrillation occurred in only 21% of patients complaining of dyspnea. Patient's age, complaint preceding the arrest and the initial cardiac rhythm associated with the arrest all possessed an independent and significant relation to survival.

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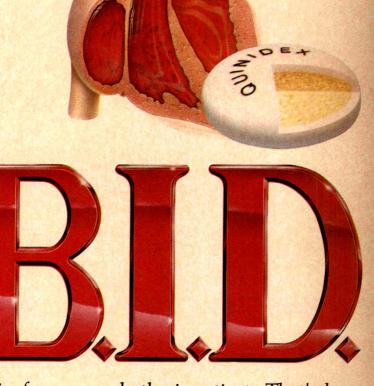
#### **Changes in Cardiac Output Determined by Continuous-Wave Doppler Echocardiography During Propafenone or Mexiletine Drug Testing**

Helmut Lange, Steven Lampert, Martin St. John Sutton, and Bernard Lown

To assess whether continuous-wave Doppler echocardiography can detect changes in forward blood flow due to the negative inotropic effects of antiarrhythmic drugs, we measured peak flow velocity in the ascending aorta, the flow velocity integral (stroke distance), the rate-corrected stroke distance and minute distance (stroke distance × heart rate) during 11 drug trials with mexiletine and 9 drug trials with propafenone. Day-to-day variability of Doppler parameters was determined before drug testing in 16 patients. Treatment with propagenone, a drug with moderate negative inotropic activity, was associated with a significant decline in Doppler parameters, while treatment with mexiletine, a drug with minimal negative inotropic activity, was not. In 5 of 9 patients treated with propagenone, the decrease in rate-corrected stroke distance exceeded the day-to-day variability, which was  $\pm$  13%. Continuous-wave Doppler echocardiography may be useful to monitor antiarrhythmic drug-induced changes in forward blood flow.

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(Quinidine Sulfate Extendedrelease Tablets, USP) 300 mg

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Please see adjacent page for brief summary.

#### **QUINIDEX EXTENTABS**

(Quinidine Sulfate Extendedrelease Tablets, USP) 300 mg

The following is a brief summary only. Before prescribing, see complete prescribing information in Quinidex product labeling.

information in Quinidex product labeling.

Contraindications: Intraventricular conduction detects. Complete A-V block. A-V conduction disorders caused by digitalis intoxication. Aberrant impulses and abnormal rightms due to escape mechanisms. Idiosyncrasy or hypersensitivity to quinidime or related cinchrons derivatives. Myabrahia gravis.

Warnings: In the treatment of afrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio, resulting in an externelly rapid ventricular rate. This possible hazard may be deduced by digitalization prior to administration of quinidine.

Reports in the literature indicate that serum concentrations of digoxin may increase and may even double when quindine is administred concurrently. Patients on concomilant therapy should be carefully monitored for digitalis toxicity. Reduction of digitorio dosage may have to be considered.

digioxin dosage may have to be considered.

Manifestations of quinifidine cardiotoxicity such as excessive prolongation of the Q interval, without a considered cardiotoxicity such as excessive prolongation of the QC interval, witening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monoticing.

onitoring. In susceptible individuals, such as those with marginally compensated cardiovascular

In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of carriac function manifested by hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.

Quinidine should be used with extreme caution in patients with incomplete AV block since complete AV block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication.

Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in serum, leading to toxicity. Patients taking quinidine occasionally have synogoal episodes which usually result from vertricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or serum levels. Synopaci episodes which synonates pontaneously or in response to freatment, but sometimes are latal.

Cases of hepatoloxocity, including granuformatous hepatitis, due to quinidine

related to dose or serum levels. Syncopal episodes frequently terminate spontaneously in response to treatment, but sometimes are statal.

Cases of hepatoloxocity, including granulomatous hepatilis, due to quinidine hypersensitivity have been reported. Unexplained lever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatoloxicity. Monitoring liver function during the first 4—8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity. Precautions: General—All the precautions applying to regular quinidine therapy apply to this product Phypersensitivity or anaphylacidir reactions to quinidine, although rare, should be considered, especially during the first weeks of therapy. Hospitalization for close critical observation, electrocardiorganic monitoring, and determination of serum quinidine levels are indicated when large doses of quinidine are used or with paleints who present an increased risk.

Information for Patients—As with all solid dosage medications, Dunindex Electralss Should be taken with an adequate amount of full, orderelasy with the patient in an upright position to facilitate swallowing. They should be swallowed whole in order to preserve the controller-telesce mechanism.

\*Laboratory\* Tests—Periodic blood counts and liver and kidney function tests should be deviationed or or reand dysfunction occurs.

preserve the controlled-release mechanism.

Laboratory Tests—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy; the drug should be discontinued if blood dyscrasias or evidence of hepatic or renal dysfunction occurs.

Drug Internactions

Unindine with achiolinergic drugs
Quinidine with cholinergic drugs
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, hizafod diuretics
Quinidine with coursering anticoagulants
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Quinidine with ranitidine

Increased serum concentration of

Quindine with rantidine
Premature ventricular contractions
and/or bigeniny
Increased quinidine half-life and an increase in
serum quindine level; potential
hypotensive reactions
Quinidine with nifedipine
Carcinogenesis: Studies in animals have not been performed to evaluate the carcino-

Carcinogenesis: Studies in animals have not been performed to evaluate the carcino genic potential of quinidine. Pregnancy, Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidex Estentabs should be administered to pregnant woman only if clearly indicated. Monteratogenic Effects: Like quinine, quinidine has been reported to have oxylocic properties. The significance of this property in the clinical setting has not been established.

established. Labor and Delivery—There is no known use for Quinidex Extentabs in labor and Gelivery However, quinidine has been reported to have oxylocic properties. The significance of this property in the clinical setting has not been established. Nursing Mothers—Because of passage of the drug into breast milk, caution should be exercised when Quinidex Extentabs are administered to a nursing woman. Pediatric Use—There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinidex Extentabs in children. Adverse Reactions: Symptoms of cinchonism, such as ringing in the ears, loss of hearing, dizingess, lightheadedness, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects in quintine are naterininestinal.

appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quintificar are gastrointestinal.

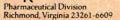
Gastrointestinal.—Naussa, vomiting, abdominal pain, diarrhea, ancrexia, granulomatous heapitis (which may be preceded by trevel, sosphagitis).

Cardiovascular.—Ventricular extrasystoles occurring at a tale of one or more every 6 normal beats, widening of the QRS complex and prolonged QT interval; complete A-V block, ventricular latificar lating and fibrillation, ventricular fulter, torsade de pointes;

block ventricular tazhycardia and fibrillation; ventricular flutter; torsade de pointes; arterial embolism; hypotension; syncope. \*\*Central Nervous System—Headache, vertigo, apprehension, excitement, confusion, delirium, dementia, ataxia, depression. \*\*Ophthalmologic and Otologic—Disturbed hearing (linnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scolomata), opin enuritis, reduced visual field. \*\*Dermatologic—Cutaneous flushing with intense pruritus, photosensitivity urticaria, rash, ezerna, edicitative ruptions, psporasis, abnormalities of pigmentation. \*\*Hypersensitivity—Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatoloxicity, granulomatous hepatitis; [See Warnings), purpura, vascultis, \*\*Hematologic—Thrombocytopenia, thrombocytopenic purpura, agranulocytosis, acute hemolytic anemia, hypoprothrombinemia, leukocytosis, shift to left in WBC differential, neutropenia.

Rev. October 1987

#### A-H-ROBINS





#### CLASSIFIED

#### CARDIOLOGIST

NON INVASIVE BC/BE INTERESTED IN ALL ASPECTS OF CLINICAL CARDIOLOGY. TO JOIN A BUSY AND RESPECTED SOLO CARDIOLO-GIST IN NORTH CENTRAL NORTH CAROLINA. EXCELLENT GROWTH POTENTIAL, SALARY, FRINGE BENEFITS, EVENTUAL PARTNERSHIP. PLEASE REPLY: BOX 1080, THE AMERICAN JOURNAL OF CARDIOLOGY, 249 W. 17th ST., NEW YORK, N.Y. 10011.

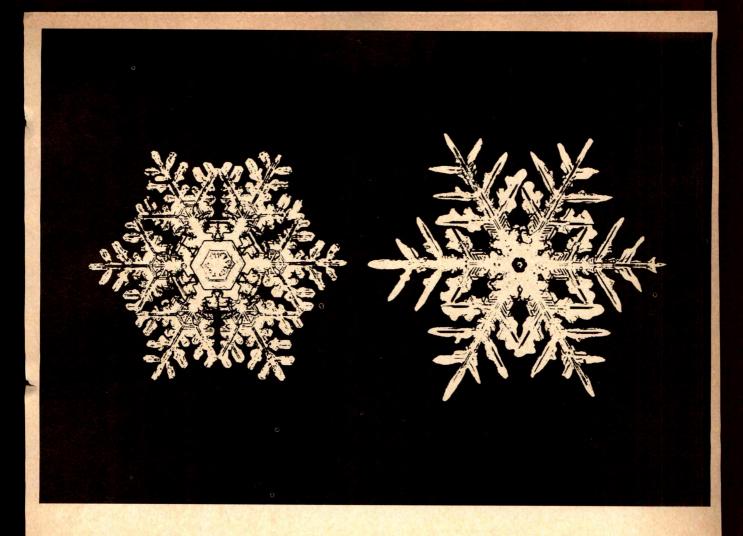
INVASIVE CARDIOLOGIST—Prestigious twelve man group located in beautiful mountainous Southeast is seeking second invasive cardiologist. Busy ready-made practice, excellent income guarantee, state university academic affiliation, one in eight call coverage. Call Janet Botton at 1-800-776-5776.

#### **CARDIOLOGISTS**



Several vacancies exist for board-certified Cardiologists in the U.S. Army Medical Department. Unique professional opportunities are available at locations in the United States and overseas. Interested individuals must not have attained their 52nd birthday. For further information on benefits and professional opportunities, call LTC Touchard at (303) 361-3208. Call collect.

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## No two are exactly alike.

Because body chemistry differs from person to person, we often need a choice of drugs to treat the same illness. You've heard it said that no two snowflakes are exactly alike. The variety is endless. Much the same is true of the human body.

Take the case of two patients suffering from hypertension. Both under the care of the same physician, who prescribes the same medication for each. One patient responds to the medication while the other reports unpleasant side-effects. Thanks to the diversity of drugs available to treat this illness, the doctor is able to prescribe another medicine that works without the side effects.

To maintain the high standards of quality care, and because some drugs work better than others on different people, it is essential to have this diversity.

America's research-based pharmaceutical companies are committed to providing a wide range of drugs of the highest quality to serve the public. Why? Because the public is made up of different people requiring different treatment—even when they suffer from the same illness.

#### Pharmaceutical Manufacturers Association

IF A NEW MEDICINE CAN HELP, WE'RE WORKING ON IT.

#### 463

#### Electrophysiologic Determinants of Recurrent Atrial Flutter After Successful Termination by Overdrive Pacing

Heinz D. Gössinger, Peter Siostrzonek, Michael Jung, Ludwig Wagner, and Herbert Mösslacher

The ability of electrophysiologic abnormalities to predict recurrence of atrial flutter was evaluated. High right atrial stimulation was performed in 25 patients with stable atrial flutter resistant to combined digitalis and quinidine medication after restoration of sinus rhythm by overdrive pacing or eventual direct current cardioversion. Recurrence of atrial flutter was observed in 12 patients during a mean follow-up period of 17 months (range 3 to 50). A greater increase in  $S_1A_1$  intervals (47 ± 11 vs 21 ± 18 ms) as defined by comparison of the interval between the stimulus artifact and the low right atrial activation at coupling intervals of 90 and 48% of the 600-ms basic drive cycle length was associated with relapse of atrial flutter. A logistic regression analysis identified the S<sub>1</sub>A<sub>1</sub> increase to be the sole independent predictor of recurrence (p = 0.0082) while previous episodes of atrial flutter or the presence of organic heart disease were identified as dependent variables. Reclassification showed a 91% sensitivity, 92% specificity and correct classification in 92% of patients. The initiation of atrial dysrhythmia had no predictive value.

#### SYSTEMIC HYPERTENSION

#### 467

#### Antihypertensive Effect of Isradipine Administered Once or Twice Daily on Ambulatory Blood Pressure

Yves Lacourcière, Luc Poirier, Danielle Dion, and Pierre Provencher

Whole-day ambulatory blood pressure (BP) monitoring was used to compare the antihypertensive efficacy of isradipine sustained-release once daily with isradipine immediate-release given twice daily in a double-blind randomized crossover study in 76 hypertensive patients. Both isradipine sustained-release and twice daily reduced significantly the mean ambulatory BP during 24-hour, working, awake and sleep periods without heart rate significantly greater in ambulatory hypertensive patients than in normotensive patients as defined by whole-day ambulatory BP monitoring. Thus, sustained-release isradipine appears to be effective as oncedaily medication in ambulatory hypertensive patients.

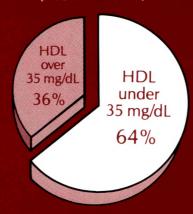
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What's a common denominator of most heart attack victims?

# HDL 35 mg/dL

Mixed hyperlipidemias—elevated cholesterol and triglycerides—are common among heart attack victims,<sup>1</sup> and nearly two-thirds of people who developed myocardial infarction in the PROCAM Trial had a low (< 35 mg/dL) baseline level of HDL cholesterol.<sup>2</sup>

HEART ATTACK PATIENTS (PROCAM TRIAL)<sup>2</sup>



# A powerful case for [OPDD BID BID (gemfibrozil) 600-mg Tablets

#### Raised low HDL 25%

—in patients whose baseline HDL was below 35 mg/dL in the landmark Helsinki Heart Study (HHS).

## Reduced heart attack incidence\* up to 62%

—in these HHS patients and 45% in HHS patients whose baseline HDL was below the median (46.4 mg/dL). Incidence of serious coronary events was similar for LOPID and placebo subgroups with baseline HDL above the median (46.4 mg/dL).

## Raised HDL levels 1½ to 3 times more effectively than lovastatin

—in a 12-week, double-blind, randomized trial among patients with moderate to severe hyperlipidemia. Lovastatin achieved greater reductions in total serum cholesterol than gemfibrozil in this study population.<sup>4</sup>

#### RAISES HDL DRAMATICALLY REDUCES HEART ATTACK

LOPID is indicated for reducing the risk of coronary heart disease (CHD) in Type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequestrants and nicotinic acid.

\*Defined as a combination of definite coronary death and/or definite myocardial infarction.

References: 1. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J Clin Invest*. 1973;52:1533-1543. 2. Assmann G, Schulte H. *PROCAM-Irial: Prospective Gardiovascular Münster Trial*. Zürich: Panscientia Verlag; 1986:8-9. 3. Data on file, Medicial Affairs Dept, Parke-Davis 4. Tikkanen MJ, Helve E, Jäättelä A, et al. Comparison between lovastatin and gemfibrozil in the treatment of primary hypercholesterolemia: the Finnish Multicenter Study. *Am J Cardiol*. 1988;62:35J-43J.

Please see last page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

Lopid® (Gemfibrozil Capsules and Tablets)

Before prescribing, please see full prescribing information. A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary

rry cirrhosis. . Preexisting gallbladder disease (See WARNINGS).

2. Preexisting galibladder disease (see WARNINGS).
3. Hypersensitivity to gemfibrozil.
WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drup Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects and aboliticis and aboliticis and subjects in the properties of the properties of the properties of the properties. jects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056). In the Helsinki Heart Study, the incidence of total malignancies discovered during the

greater frend in the Lopid group (43 vs.27 patients in the placebo group), p=0.000p.

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Logid and elsepho sub-

different between Lopid and placebo sub-groups. Follow-up of the Helsinki Heart Study participants will provide further inforcancer morbidity.

 A gallstone prevalence substudy of 450
Helsinki Heart Study participants showed a trend toward a greater prevalence of gall-stones during the study within the Lopid treatment group (7.5% vs 4.9% for the place bo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the

group treated with clothrace but chlockystectionly observed in the White Study in the group treated with clothrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in

definishment and decades into and intensitial control to the patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should

4. Concomitant Anticoagu lants - Caution should be exercised when antic

4. Concomitant Anticoagulants — Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts — Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. Initial Therapy — Laboratory studies should be done to ascertain the text of the protection of t

PRECAUTIONS. 1. Initial Therapy — Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss

tempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. Continued Therapy — Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. Drug Interactions — (A) Lovastatin: Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis and acute renal failure. There is no assurance that periodic monitoring of

lovastatin and gemilibrozii does not outweign the risks of severe myopatry, maddomyolysis, and acute renal failure. There is no assurance that periodic monitoring of
creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT
THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT
PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN NITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. Carcinogenesis, Mutagenesis, Impairment of Fertility – Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high denice of benign liver hodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offsoring.

5. **Pregnancy Category B** – Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those pa-

the and refine rats, the set of copie in pregnancy should be reserved to most partitions where the benefit clearly outweighs the possible risk to the patient or fetus.

6. Nursing Mothers — Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

fibrozi in rats, a decision should be made whether to discontinue fursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. Hematologic Changes – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months.

Lopid administration.

8. Liver Function — Abnormal liver function tests have been observed occasionally

during Lopid administration, including elevitions of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discon-tinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist. 9. Use in Children – Safety and efficacy in

children have not been established.

ADVERSE REACTIONS. In the double-blind ntrolled phase of the Helsinki Heart Study, 46 patients received Lopid for up to 5 years In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in paren-

theses): gastrointestinal reactions. 31,296 (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically continued in most cases where data are available), 1.2% (0.6%); atrial

(histologically confirmed in most cases where data are available), 1.2% (U6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but

adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular

where a causal relationship was not established include cataracts, periprieral vascular disease, and intracerebral hemorrhage. From other studies it seems probable that Lopid is causally related to the occurrence of musculoskeletal symptoms (See WARNINGS), and to abnormal liver function tests and hematologic changes (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients. Additional adverse reactions that have been reported for gemfibrozil are listed below.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:
CAUSAL RELATIONSHIP PROBABLE: Gastrointestinal: cholestatic jaundice; Central Nervous System: dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; Eye: blurred vision; Genitourinary: impotence; Musculoskeletal: myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); Clinical Laboratory: increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase Hematopoietic: anemia, leukopenia, bone marrow hypoplasia, eosinophilia; Immunologic: angioedema, laryngeal edema, urticaria, Integumentary: exfoliative dermatitis; spruritus.

matitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: General: weight loss; Cardiac: extrasystoles; Gastrointestinal: pancreatitis, hepatoma, colitis; Central Nervous System: confusion, convulsions, syncope; Eye: retinal edema; Genitourinary: decreased male fertility. Clinical Laboratory: positive antinuclear antibody; Hematopoietic: thrombocytopenia; Immunologic: anaphylaxis, Lupus-like syndrome, vasculitis; Integumentary: alopecia

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg
administered in two divided doses 30 minutes before the morning and evening meal

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

MANAGEMENT OF OVERDOSE. While there has been not reported case or overdosage, symptomatic supportive measures should be taken should it occur. References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfilbrozil in middle-aged men with dyslipidemia. N Engl J Med 1987:317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. JAMA 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B et al. (eds.): The Metabolic Basis of Inherited Disease, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.

Caution — Federal law prohibits dispensing without prescription.

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PD-56-IA-5860-P-1(12-89)



#### **VALVULAR HEART DISEASE**

473

#### Percutaneous Double Balloon Valvotomy for Severe Rheumatic Mitral Stenosis

Carlos E. Ruiz, John W. Allen, and Francis Y.K. Lau

Percutaneous double balloon valvotomy for severe rheumatic mitral stenosis was successfully performed in 281 of 285 patients. The mean transvalvular gradient decreased from  $16 \pm 7$  to  $5 \pm 3$  mm Hg, and the cardiac output increased from  $3.8 \pm 1.0$  to  $5.4 \pm 1.5$  liters/min, resulting in an increase of the mitral valve area from  $0.86 \pm 0.24$  to  $2.41 \pm 0.54$  cm<sup>2</sup>. Symptomatic improvement occurred in 272 of the 285 patients. There were 3 procedure-related deaths (1%) 2 of which were related to perforations of the left ventricle. Postdilatation regurgitation was not significant in the majority of patients. Therefore, this procedure can be performed at low risk with effective results and a fast recovery.

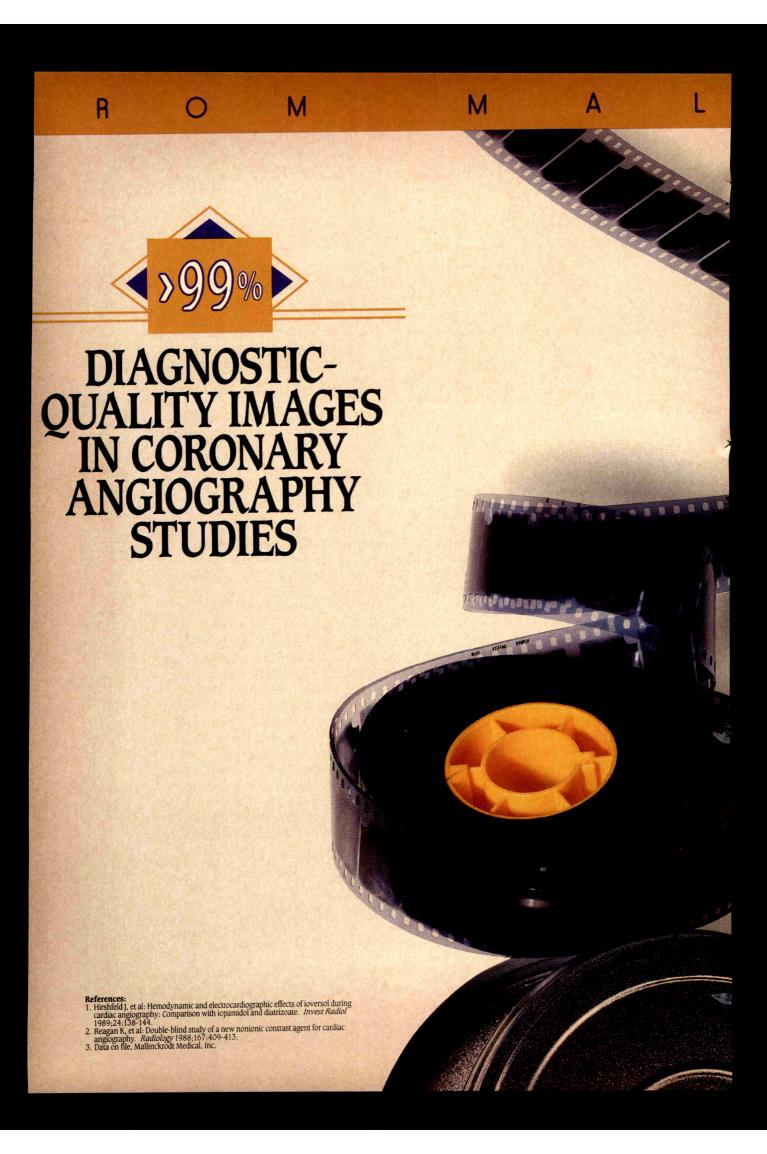
#### CARDIOMYOPATHY

478

#### Prognostic Significance of Radionuclde-Assessed Diastolic Function in Hypertrophic Cardiomyopathy

Taishiro Chikamori, Shaughan Dickie, Jan D. Poloniecki, Melvyn J. Myers, J. Peter Lavender, and William J. McKenna

To evaluate the prognostic significance of diastolic function in hypertrophic cardiomyopathy, technetium-99m gated equilibrium radionuclide angiography was performed in 161 patients. Five diastolic indexes were calculated. During 3.0 ± 1.9 years, 13 patients had disease-related mortality. Stepwise discriminant analysis revealed that young age, syncope at diagnosis, peak ejection rate, family history, peak filling rate, relative filling volume by peak filling rate and pattern of left ventricular hypertrophy were the most statistically significant (p = 0.0001) predictors of disease-related mortality. Discriminant analysis excluding the diastolic indexes, however, showed similar predictability. To obtain more homogenous groups for analysis, patients were classified as survivors, electrically unstable and heart failure death or cardiac transplant. None of the diastolic indexes achieved statistical differences between the groups. Radionuclide assessment of diastolic function did not improve predictability for 3year mortality or contribute to the identification of patients at increased risk of sudden death.



In clinical studies involving patients undergoing coronary arteriography and left ventriculography, OPTIRAY 320 produced diagnostic-quality images in 100% of cases, 94.7% of which were rated excellent or good. 1-3

Overall radiographic quality: Coronary arteriography with left ventriculography 1-3			
Contrast Medium	No. of Patients	No. of Procedures Good or Excellent	No. of Procedures Rated Diagnostic
OPTIRAY 320	190	180 (94.7%)	190 (100%)
Iopamidol-370	78	77 (98.7%)	78 (100%)
Diatrizoate-370	79	75 (94.9%)	79 (100%)

#### **Indications for OPTIRAY**

OPTIRAY 320 is indicated for a broad range of cardiac imaging procedures, including:

Coronary arteriography and left ventriculography

Peripheral arteriography

Aortography, visceral and renal arteriography

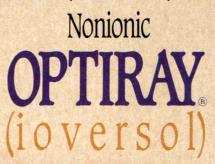
Cerebral arteriography

OPTIRAY 160 is indicated for intra-arterial digital subtraction angiography (IA-DSA).

All nonionic iodinated contrast media currently available inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary to minimize thromboembolic events.

Osmolali	ty and viscosity of nonio	nic contrast agents	
Contrast Medium	Concentration (mg Iodine/mL)	Osmolality (mOsm/kg H <sub>2</sub> O)	Viscosity at 37°C (CPS)
Iopamidol*	370	796	9.4
Iohexol <sup>†</sup>	350	844	10.4
OPTIRAY 320§	320	702	5.8
OPTIRAY 240	240	502	3.0
OPTIRAY 160	160	355	1.9

\* Marketed by Squibb Diagnostics under license from Bracco Industria Chimica, S.p.A., Italy. †Marketed by Winthrop Pharmaceuticals under license from Nycomed AS, Norway. §Marketed by Mallinckrodt Medical, Inc. in the U.S.A.





#### THE PERCENTAGES ARE IN YOUR FAVOR

#### OPTIRAY® 160 240 320 (loversol Injection)

DESCRIPTION: Each milliliter of OPTIRAY 160 (loversol injection 34%) provides 339 mg of loversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 160 provides 16% (160 mg/mL) organically bound iodine.

Each milliliter of OPTIRAY 240 (loversol injection 51%) provides 509 mg of loversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 240 provides 24% (240 mg/mL) organically bound iodine

organically bound iodine.

Each milliliter of OPTIRAY 320 (ioversol injection 68%) provides 678 mg of conversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 320 provides 32% (320 mg/mL) organically bound iodine.

#### CONTRAINDICATIONS: None

WARNINGS: Nonionic iodinated contrast media inhibit blood

WARNINGS: Nonionic iodinated contrast media inhibit blood cagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intra-vascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state and concomitant medications may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended including close attention to

development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended including close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinized saline solutions and minimizing the length of the procedure. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of in vitro clotting.

Serious or fatal reactions have been associated with the administration of iodine-containing radiopaque media. It is of utmost importance to be completely prepared to treat any contrast medium reaction.

As with any contrast medium, serious neurologic sequelae, including permanent paralysis, can occur following cerebral arteriography, selective spinal arteriography and arteriography of vessels supplying the spinal cord. A cause-effect relationship to the contrast medium mas not been established since the patients' pre-existing condition and procedural technique are causative factors in themselves. The arterial injection of a contrast medium should never be made following the administration of vasopressors since

causative factors in themselves. The arterial injection of a contrast medium should never be made following the administration of vasopressors since they strongly potentiate neurologic effects.

Caution must be exercised in patients with severely impaired renal function, combined renal and hepatic disease, severe thyrotoxicosis, myelomatosis, or anuria, particularly when large doses are administered. Intravascularly administered iodine-containing radiopaque media are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly in those with therapeutically resistant anurian Myeloma occurs most commonly in persons over age 40. Although neither the contrast agent nor dehydration has been proved separately to be the cause of anuria in myelomatous patients; it has been speculated that the combination of both may be causative. The risk in myelomatous patients is not a contrandication to the procedure. however, special precautions, including maintenance of normal hydration and close monitoring, are required. Partial dehydration in the preparation of these patients prior to injection is not recommended since this may predispose the patient to precipitation of the myeloma protein.

Administration of radiograpue materials to patients known or suspected of having pheochromocytoms should be performed with extreme caution.

of having pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The blood pressure should be assessed throughout the procedure, and measures for treatment of a hypertensive crisis should be available.

Contrast media may promote sickling in individuals who are homozygous

Contrast media may promote sciking in individuals who are no mozygous for sickle cell disease when administered intravascularly.

Reports of thyroid storm following the intravascular use of iodinated radiopaque agents in patients with hyperthyroidism or with an auton-omously functioning thyroid nodule, suggest that this additional risk be evaluated in such patients before use of any contrast medium.

PRECAUTIONS: General: Diagnostic procedures which involve the use of iodinated intravascular contrast agents should be carried out under the direction of personnel skilled and experienced in the particular procedure to be performed. A fully equipped emergency cart, or equivational supplies and equipment, and personnel competent in recognizing and treating adverse reactions of all types should always be available. Since severe delayed reactions have been known to occur, emergency facilities and competent personnel should be available for at least 30 to 60 minutes after administration.

administration
Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, diabetic patients, and in susceptible non-diabetic patients (often elderly with pre-existing renal disease). Patients should be well hydrated prior to and following the administration of OPTIRAY.
The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions, should always be considered (See ADVERSE REACTIONS). Increased risk is associated with a history of previous reaction to a contrast medium, a known sensitivity to iodine and known allergies (i.e., bronchial asthma, hay fever and food allergies) or hypersensitivities.

and known altergies (i.e., bronchial asthma, hay fever and food altergies) or hypersensitivities.

The occurrence of severe idiosyncratic reactions has prompted the use of several pretesting methods. However, pretesting cannot be relied upon to predict severe reactions and may itself be hazardous to the patient. It is suggested that a thorough medical history with emphasis on altergy and hypersensitivity, prior to the injection of any contrast medium, may be more accurate than pretesting in predicting potential adverse reactions. A positive history of altergies or hypersensitivity does not arbitrarily contrainteate the use of a contrast agent when a diagnostic procedure is thought essential, but caution should be exercised. Premedication with antihistamines or corticosteroids to avoid or minimize possible altergic reactions in such patients should be considered. Reports indicate that such pretreatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity.

General anesthesia may be indicated in the performance of some procedures in selected patients; however, a higher incidence of adverse reactions has been reported in these patients, and may be attributable to the inability of the patient to identify untoward symptoms or to the hypotensive effect of anesthesia which can prolong the circulation time and increase the duration of exposure to the contrast agent.

In angiographic procedures, the possibility of dislodging plaques or damaging or perforating the vesses wall should be considered during cather manipulations and contrast medium injection. Test injections to insure proper catheter placement are suggested.

Angiography should be avoided whenever possible in patients with homocystinuria because of the risk of inducing thrombosis and embolism.

Patients with congestive heart failure should be observed for several hours following the procedure to detect delayed hemodynamic

disturbances which may be associated with a transitory increase in the circulating osmotic load.

Selective coronary arteriography should be performed only in selected patients and those in whom the expected benefits outweigh the procedural risk. The inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure.

risk. The inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure.

Extreme caution during injection of a contrast medium is necessary to avoid extravasation. This is especially important in patients with severe arterial or venous disease.

Drug Interactions: Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by intravascular contrast agents. Administration of any intravascular contrast agents. Administration of any intravascular contrast agents contrast agents. Administration of any intravascular contrast agents. Other drugs should not be mixed with loversol injection.

Drug Laboratory Test Interactions: The results of PBI and radioactive iodine uptake studies, which depend on lodine estimation, will not accurately reflect thyroid function for up to 16 days following administration of iodine estimations, e.g., T3 resin uptake and total or free thyroxine (T4) assays are not affected.

Carcinogenesis. Mutagenesis, Impairment of Fertility: No long term animal studies have been performed to evaluate carcinogenic potential However, animal studies suggest that this drug is not mutagenic and does not affect fertility.

Pregnancy Caregory B: No teratogenic effects attributable to ioversol have been observed in teratology studies performed in animals. There are, however, no adequate and well controlled studies in pregnant women. It is not known whether ioversol crosses the placental barrier in humans and appear to enter fetal tissues passively. Because animal eratology studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. X-ray procedures involve a certain risk related to the exposure of the fetus.

Mursing Mothers: It is not known whether ioversol is excreted unchanged in human milk. However, many injectable contrast agents are excreted unchanged in human milk. However, many injectable c

ADVERSE REACTIONS: Adverse reactions following the use of OPTIRAY formulations are usually mild to moderate, of short duration and resolve spontaneously (without treatment). However, serious, life-threatening and fatal reactions, mostly of cardiovascular origin, have been associated with the administration of iodine-containing contrast

media.
Injections of contrast media are often associated with sensations of warmth and pain. In controlled double-blind clinical studies, significantly less warmth and pain were associated with the injection of OPTIRAY than with iothalamate meglumine, distrizoate meglumine, and diatrizoate meglumine and diatrizoate sodium.

with iothalamate meglumine, diatrizoate meglumine, and diatrizoate meglumine and diatrizoate sodium.

When OPTIRAY 320 is used for coronary arteriography and ventriculography in double-blind clinical trials, electrocardiographic and hemotynamic changes occur with less frequency and severity with ioversol injection than with diatrizoate meglumine and diatrizoate sodium. Following coronary artery and left ventricular injection, electrocardiographic parameters were affected less with OPTIRAY (ioversol injection) han with diatrizoate meglumine and diatrizoate sodium injection. These parameters included the following: bradycardia, tachycardia, T-wave amplitude. ST depression and ST elevation.

OPTIRAY has also been shown to cause fewer changes in cardiac function and systemic blood pressure than conventional ionic media. These include cardiac output, left ventricular systolic and end-diastolic pressures. Include cardiac output, left ventricular systolic and pulmonary artery systolic pressures and decreases in systolic and diastolic blood pressures. The following table of incidence of reactions is based upon clinical trials with OPTIRAY formulations in over 1100 patients. This listing includes all adverse reactions which were coincidental to the administration of ioversol regardless of their direct attributability to the drug or the procedure. Adverse reactions are listed by organ system and in decreasing order of occurrence. Significantly more severe reactions are listed before others in a system repardless of frequency.

System	> 1%	eactions < 1%
Cardiovascular	none	angina pectoris hypotension vascular spasm bradycardia conduction defect false aneurysm hypertension transient arrhythmia vascular trauma
Digestive	none	nausea vomiting
Nervous	none	cerebral infarct headache blurred vision vertigo lightheadedness vasovagal reaction disorientation dysphasia paresthesia visual hallucination
Respiratory	none	laryngeal edema nasal congestion sneezing coughing hypoxia
Skin	none	periorbital edema urticaria facial edema flush pruritus
Miscellaneous	none	extravasation shaking chills bad taste

bad taste general pain Regardless of the contrast medium employed, the overall incidence of serious adverse reaction is higher with coronary arteriography than with other procedures. Cardiac decompensation, serious arrhythmias, myocardial ischemia or myocardial infarction may occur during coronary arteriography and left ventriculography. General Adverse Reactions to Contrast Media. The following adverse reactions are possible with a contraction of the contraction o

The following adverse reactions are possible with any parenterally administered iodinated contrast medium. Severe life-threatening reactions and fatalities, mostly of cardiovascular origin, have occurred. Most deaths

occur during injection or 5 to 10 minutes later; the main feature being car-diac arrest with cardiovascular disease as the main aggravating factor. Iso-lated reports of hypotensive collapse and shock are found in the literature. Based upon clinical literature, reported deaths from the administration of conventional iodinated contrast agents range from 6.6 per 1 million (0.00066 percent) to 1 in 10,000 patients (0.01 percent).

(U. Duodo percent) to 1 in 10,000 patients (U. U.) percent).
The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that of the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

Adverse reactions to injectable contrast media fall into two categories:

Adverse reactions to injectable contrast media fail into two categories: chemotoxic reactions and diosyncratic reactions. Chemotoxic reactions result from the physicochemical properties of the contrast medium, the dose and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more fre-

lotosyncratic reactions include all other reactions. They occur more fre-quently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the dose injected, the speed of injection, the mode of injection and the radiographic procedure. Idiosyncratic reactions are sub-divided into minor, intermediate and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening

and treatment is urgent and mandatory.

In addition to the adverse reactions reported for ioversol, the following additional adverse reactions have been reported with the use of other contrast agents and are possible with any water soluble, iodinated con-

Ask agent. Mervous: muscular spasm, convulsions, aphasia, syncope, paralysis, isual field losses which are usually transient but may be permanent, coma

Cardiovascular: angioneurotic edema, peripheral edema, vasodilation, thrombosis and rarely thrombophlebitis, disseminated intravascular

coagulation and shock.

Skin: maculopapular rash, erythema, conjunctival symptoms, ecchymo-

coagulation and shock.

Skin: maculopapular rash, erythema, conjunctival symptoms, ecchymosis and tissue necrosis.

Respiratory: choking, dyspnea, wheezing which may be an initial manifestation of more severe and infrequent reactions including asthmatic attack, laryngospasm and bronchospasm, pulmonary edema, apnea and cyanosis. Rarely these allergic-type reactions can progress into anaphylaxis with loss of consciousness, coma, severe cardiovascular disturbances and death.

Miscellaneous: hyperthermia, temporary anuria or other nephropathy. Other reactions may also occur with the use of any contrast agent as a consequence of the procedural hazard; these include hemorrhage or pseudoaneurysms at the puncture site, brachial plexus palsy following axillary artery injections, chest pain, myocardial infarction, and transient changes in hepatorenal chemistry tests. Arterial thrombosis, displacement of arterial plaques, venous thrombosis, dissection of the coronary vessels and transient sinus arrest are rare complications.

In cerebral arteriography, cardiovascular reactions that may occur with some frequency are bradycardia and either an increase or decrease in systemic blood pressure. Neurological reactions that may occur with some frequency are bradycardia and either an increase or decrease in systemic blood pressure. Neurological reactions that may occur are seizures, drowsiness, transient paresis, and mild disturbances in vision. Central nervous system reactions with OPTIRAY in controlled clinical studies in cerebral arteriography that occurred with frequencies greater than 1% were vertigo (4%) and blurred vision (3%).

In aortography, depending on the technique employed, the risks of this procedure also include the following: injury to the aorta and neighboring organs, pleural puncture, renal damage including infarction and acute tubular necrosis with oliginia and anuria, ritroperitoneal hemorrhage from the translumbar approach and spinal cord injury and pathology associated with the syndrome of transevers myelits

#### PRECAUTIONS FOR SPECIFIC PROCEDURES:

Cerebral Arteriography
Extreme caution is advised in patients with advanced arteriosclerosis, severe hypertension, cardiac decompensation, senility, recent cerebral thrombosis or embolism, and migraine.

Peripheral Arteriography
Pulsation should be present in the artery to be injected. In thromboangiitis obliterans, or ascending infection associated with severe ischemia, angiography should be performed with extreme caution, if at all.

Coronary Arteriography and Left Ventriculography
Mandatory prerequisites to the procedure are specialized personnel, ECG
monitoring apparatus and adequate facilities for immediate resuscitation
and cardioversion. Electrocardiograms and vital signs should be routinely
monitored throughout the procedure.

Venography
Special care is required when venography is performed in patients with
suspected thrombosis, phlebitis, severe ischemic disease, local infection
or a totally obstructed venous system. In order to minimize extravasation
during injection, fluoroscopy is recommended.

OVERDOSAGE: The adverse effects of overdosage are life threatening and affect mainly the pulmonary and cardiovascular system. Treatment of an overdosage is directed toward the support of all vital functions, and prompt institution of symptomatic therapy, loversol does not bind to plasma or serum protein and is therefore,

The intravenous LD<sub>50</sub> values (gl/kg) for ioversol in animals were: 17 (mice), and 15 (rats).

DOSAGE AND ADMINISTRATION: Details on dosage are provided in the package insert. CONSULT FULL PACKAGE INSERT BEFORE USE.



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#### Anti-Beta-Receptor Antibodies in Human Dilated **Cardiomyopathy and Correlation with HLA-DR Antigens**

Constantinos J. Limas, Catherine Limas, Spencer H. Kubo, and Maria-Teresa Olivari

Autoantibodies against the cardiac  $\beta$ -adrenergic receptor are present in approximately 30% of patients with idiopathic dilated cardiomyopathy and can be detected using ligand-binding inhibition, immunoprecipitation or immunoblotting. The presence of antireceptor antibodies is strongly linked to the HLA-DR4 phenotype: 73% of the HLA-DR4 dilated cardiomyopathy patients in this series had such antibodies compared to 22% of HLA-DR4-negative patients. Conversely, 67% of the antireceptor-antibody-positive patients typed as HLA-DR4 compared to only 10% of the antibody-negative patients. The HLA-DR3 phenotype was absent in antibody-positive patients but present in 37% of antibody-negative patients. These results suggest that the development of anti-β-receptor antibodies in patients with idiopathic dilated cardiomyopathy is under the control of the major histocompatibility locus.

#### CONGENITAL HEART DISEASE

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Bradycardia-Mediated Tachyarrhythmias in Congenital Heart Disease and Responses to Chronic Pacing at Physiologic Rates Michael J. Silka, James R. Manwill, Jack Kron, and John H. McAnulty

The long-term effects of cardiac pacing on the frequency of various tachyarrhythmias associated with chronic bradycardia were evaluated in 21 young patients with congenital heart disease. Analysis was based on a direct comparison of the number of episodes of the differing tachyarrhythmias during the 12-month intervals immediately before and after pacing. Antiarrhythmic drug therapy was not altered during the initial study intervals. Significant reduction in the frequencies of supraventricular (p = 0.008) and ventricular (p = 0.02) tachyarrhythmias were observed after pacing. However, the frequency of atrial flutter was not altered. Pacing appears to provide an effective therapy for certain tachyarrhythmias associated with bradycardia, although critical modes may be necessary.

#### **MISCELLANEOUS**

#### 494

#### **Effect of Beta Adrenoceptors and Thyroid Hormones on** Velocity and Acceleration of Peripheral Arterial Flow in **Hyperthyroidism**

Denis Chemla, Jaime Levenson, Paul Valensi, Yves LeCarpentier, Jean-Claude Pourny, Isabelle Pithois-Merli, and Alain Simon

To determine the effects of thyrotoxicosis on both pulsatile and steady components of peripheral regional circulation, we studied brachial artery flow patterns in 10 hyperthyroid and 10 normal subjects using pulsed Doppler. Compared to control subjects, hyperthyroid patients had higher mean blood flow and velocity, and higher peak systolic blood acceleration. In hyperthyroid patients mechanical exclusion of the hand from brachial circulation (by inflating a cuff around the wrist) reduced mean flow and velocity while peak systolic acceleration remained unchanged. In addition, short-term selective (atenolol) and nonselective (propranolol)  $\beta_1$ -blocking treatment reduced peak systolic acceleration only. Inducement of the euthyroid state normalized mean blood velocity and flow, and peak systolic acceleration. These data suggest that mean blood velocity relates to peripheral vascular factors while peak systolic acceleration is related to intrinsic cardiac mechanisms in hyperthyroid patients.

#### Cardiac Transplantation in Patients with Preexisting **Neoplastic Diseases**

Brooks S. Edwards, Sharon A. Hunt, Michael B. Fowler, Hannah A. Valantine, Edward B. Stinson, and John S. Schroeder

In the last 4 years at Stanford University Medical Center, 8 cardiac transplants have been performed in 7 patients with a history of neoplastic disease. At an average follow-up of over 2 years, there has been only 1 case of recurrent neoplasia. Immunosuppressive therapy in these patients apparently did not increase the risk for neoplastic recurrence. The current study demonstrates that, in a carefully selected group, previously treated neoplastic disease does not represent a contraindication to cardiac transplantation.

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#### 505

#### Normal Values for Noninvasive Estimation of Left Ventricular **Contractile State and Afterload in Children**

Rodney C.G. Franklin, Richard K.H. Wyse, Thomas P. Graham, Vanda M. Gooch, and John E. Deanfield

The outcome and suitability for therapeutic interventions in children with congenital heart disease are dependent on adequate left ventricular function, but changing loading conditions make it difficult to assess ventricular contractility using conventional load-dependent indexes. Using echocardiography, we studied left ventricular morphometrics and contractility in 44 normal children, aged 2 to 12 years. All morphometric indexes, volumes and mass increased linearly with age and body surface area (p < 0.001 in all). Systolic function and endocardial and mid-wall meridional and circumferential stress remained constant. A load-independent measure of the normal resting left ventricular contractile state was determined by relating the rate-corrected velocity of circumferential fiber shortening to endsystolic endocardial meridional and circumferential stress. There was an inverse linear correlation (r = -0.641 and -0.557, respectively, p <0.001). These data provide a quantitative basis for assessment of myocardial hypertrophy, afterload and contractile state in childhood.

#### **BRIEF REPORTS**

Usefulness of Silent Ischemia, Ventricular Tachycardia, and Complex Ventricular Arrhythmias in Predicting New Coronary **Events in Elderly Patients with Coronary Artery Disease or Systemic Hypertension** 

Wilbert S. Aronow and Stanley Epstein

#### 513

**Left Main Coronary Artery Disease Progression After Percutaneous Transluminal Coronary Angioplasty** 

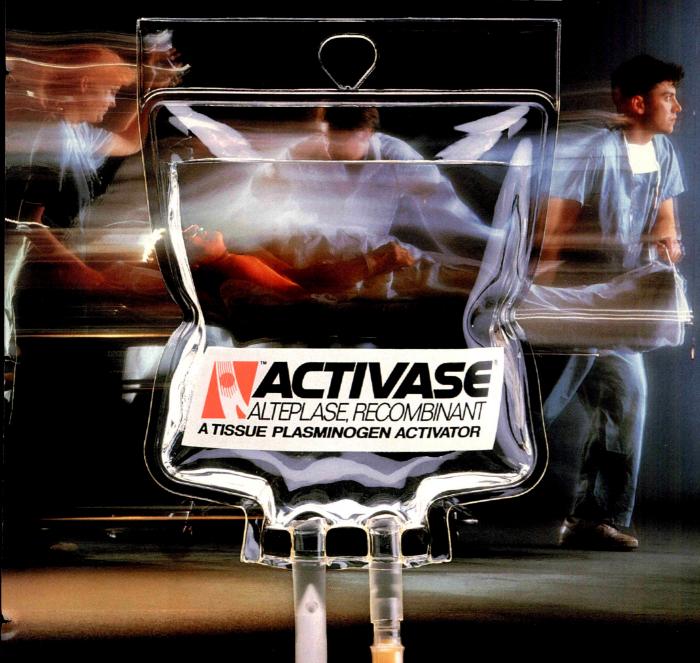
Catherine M. Kells, Robert M. Miller, Mark A. Henderson, Judy M. Lomnicki, and Robert G. Macdonald

Differential Hemodynamic Effects of Oral Enoximone in Severe **Congestive Heart Failure** 

Srinivas Murali, Barry F. Uretsky, Anita R. Betschart, Tammy R. Tokarczyk, Judy A. Kolesar, and P. Sudhakar Reddy

**IN ACUTE MI** 

# OPTIMIZE CONTROL WHEN A LIFE IS ON THE LINE



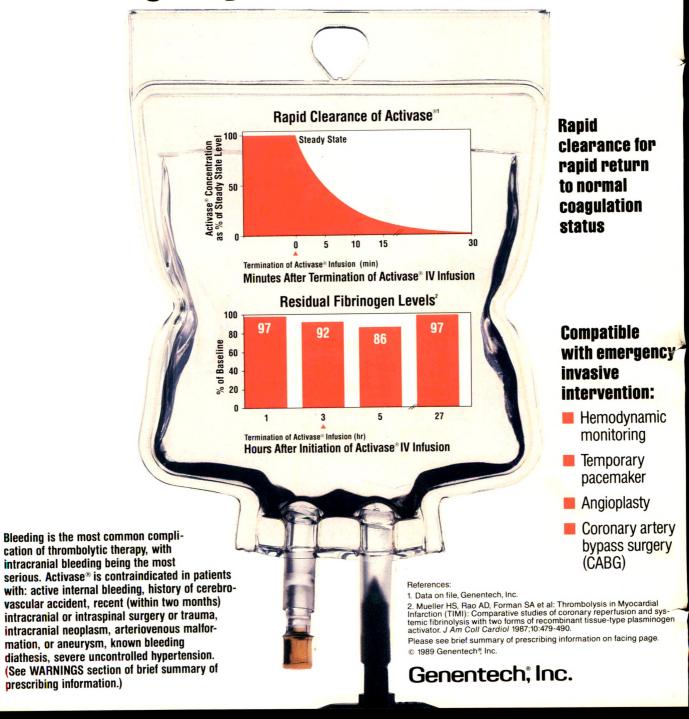
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Genentech, Inc.

#### When a life is on the line



# Four-minute half-life and fibrin specificity compatible with emergency invasive intervention





Brief Summary Consult full prescribing information before using.

INDICATIONS AND USAGE: ACTIVASE® is indicated for use in the management of acute myocardial INDICATIONS AND USAGE: ACTIVASE® is indicated for use in the management of acute myocardial infarction (AMI) in adults for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms.

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, ACTIVASE® is contraindicated in the following situations: • Active internal bleeding • History of cerebrovascular accident • Recent (within two months) intracranial or intraspinal surgery or trauma (see WARNINGS) • Intracranial neoplasm, arteriovenous malformation, or aneurysm • Known bleeding ditahesis • Severe uncontrolled hunertension.

WARNINGS) - Intracranial neoplasm, arteriovenous malformation, or aneurysm - Known bleeding diathesis - Severe uncontrolled hypertension.

WARNINGS: Bleeding The most common complication encountered during ACTIVASE® therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: - Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites - Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

Concomitant use of heparin anticoagulation may contribute to bleeding. Some hemorrhagic episodes occurred one or more days after the effects of ACTIVASE® had dissipated, but while heparin therapy was continuing.

was continuing.

As fibrin is lysed during ACTIVASE® therapy, bleeding from recent puncture sites may occur. 
Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including sites of catheter insertion, arterial and venous puncture, cutdown and needle puncture). 
Intramuscular injections and nonessential handling of the patient should be avoided during treatment with ACTIVASE® Venipunctures should be performed carefully and only as required. 
Should an arterial puncture be necessary during an infusion of ACTIVASE® it is preferable to use an upper extensity typical expectable to use and the proposed of the properties of the proposed of the p

Should an arterial puncture be necessary during an infusion of ACTIVASE\* it is preferable to use an upper extremity vessel accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding. Should serious bleeding (not controllable by local pressure) occur, the infusion of ACTIVASE\* and any concomitant heparin should be terminated immediately. Each patient being considered for therapy with ACTIVASE\* should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy. In the following conditions, the risks of ACTIVASE\* therapy may be increased and should be weighed against the anticipated benefits: \*Recent (within 10 days) major surgery, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels \*Cerebrovascular disease \*Recent (within 10 days) gastrointestinal or genitourinary bleeding \*Recent (within 10 days) trauma \*Hypertension: systolic BP≥180 mm Hg and/or diastolic BP≥110 mm Hg \*High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation \*Acute pericarditis \*Subacute bacterial endocarditis \*Hemostatic defects including those secondary to severe hepatic or renal disease \*Significant liver dysfunction \* mitral stenosis with atrial infinitation - Acute pericardrits - Subacute bacterial endocarditis - Hemostation defects including those secondary to severe hepatic or renal disease - Significant liver dysfunction - Pregnancy - Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions - Septic thrombophlebitis or occluded AV cannula at seriously infected site - Advanced age, i.e., over 75 years old - Patients currently receiving oral anticoagulants - Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

a significant hazard of would be particularly difficult to manage because of its location.

Arrhythmias Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias are not different from those often seen in the ordinary course of AMI and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of ACTIVASE® are administered.

PRECAUTIONS: General Standard management of MI should be implemented concomitantly with ACTIVASE® treatment. Noncompressible arterial puncture must be avoided. Arterial and venous punctures should be minimized. In the event of serious bleeding, ACTIVASE® and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

Readministration There is no experience with readministration of ACTIVASE® If anaphylactoid reaction occurs, infusion should be discontinued immediately and appropriate therapy initiated.

Although sustained antibody formation in patients receiving one dose of ACTIVASE® has not been documented, readministration should be undertaken with caution.

documented, readministration should be undertaken with caution.

Laboratory Tests During ACTIVASE\* therapy, results of coagulation tests and/or measures of fibrino-lytic activity may be unreliable unless specific precautions are taken to prevent in vitro artifacts. ACTIVASE\* is an enzyme that when present in blood in pharmacologic concentrations remains active under in vitro conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150-200 units/mL) can to some extent mitigate this pharmacon. extent mitigate this phenomenon.

Drug Interactions The interaction of ACTIVASE® with other cardioactive drugs has not been studied. In

addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function may increase the risk of bleeding if administered prior to, during or after ACTIVASE\* therapy.

Use of Anticoagulants Heparin has been administered concomitantly with and following infusions of ACTIVASE\* to reduce the risk of rethrombosis. Because either heparin or ACTIVASE\* alone may cause Pedago complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

Pregnancy (Category C) Animal reproduction studies have not been conducted with ACTIVASE\* It is also not known whether ACTIVASE\* can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ACTIVASE\* should be given to a pregnant woman only if clearly needed.

Pediatric Use Safety and effectiveness of ACTIVASE® in children has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which evaluated tumorigenicity of ACTIVASE® and effect on tumor metastases in rodents, were negative. Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure and only at the highest concentrations tested.

Nursing Mothers It is not known whether ACTIVASE® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ACTIVASE® is administered to a

ADVERSE REACTIONS: Bleeding The most frequent adverse reaction associated with ACTIVASE\* is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

The following incidence of significant internal bleeding (estimated as>250 cc blood loss) has been reported in studies in over 800 patients treated at all doses:

The incidence of intracranial bleeding in patients treated with ACTIVASE® Alteplase, recombinant, is as follows:

Dose	Number of Patients	%
100 mg	3272	0.4
150 mg	1779	1.3
1-1.4 mg/kg	237	0.4

These data indicate that a dose of 150 mg of ACTIVASE\* should not be used because it has been associated with an increase in intracranial bleeding.

Recent data indicate that the incidence of stroke in 6 randomized double-blind placebo controlled trials1-7 is not significantly different in the ACTIVASE\* treated patients compared to those treated with placebo (37/3161, 1.2% versus 27/3092, 0.9%, respectively) (p = 0.26).

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, ACTIVASE\* therapy should be discontinued immediately, along with any concomitant therapy with heparin.

Fibrin, which is part of the hemostatic plug formed at needle puncture sites, will be lysed during ACTIVASE\* therapy. Therefore, ACTIVASE\* therapy requires careful attention to potential bleeding sites.

Allergic Reactions No serious or life-threatening allergic reactions have been reported. Other mild hypersensitivity reactions such as urticaria have been observed occasionally.

Other Adverse Reactions Other adverse reactions have been reported, principally nausea and/or vomiting, hypotension, and fever. These reactions are frequent sequelae of MI and may or may not be attributable to ACTIVASE\* therapy.

DOSAGE AND ADMINISTRATION: Administer ACTIVASE® as soon as possible after the onset

of symptoms.

ACTIVASE\* is for intravenous administration only.

The recommended dose is 100 mg administered as 60 mg (34.8 million IU) in the first hour (of which 6 to 10 mg is administered as a bolus over the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 mg (11.6 million IU) over the third hour. For smaller patients (less than 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.\*

#### A DOSE OF 150 MG OF ACTIVASE® SHOULD NOT BE USED BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Although the use of anticoagulants and antiplatelet drugs during and following administration of ACTIVASE® has not been shown to be of unequivocal benefit, heparin has been administered concomitantly for 24 hours or longer in more than 90% of patients. Aspirin and/or dipyridamole have been given either during and/or following heparin treatment.

Reconstitution and Dilution DO NOT USE IF VACUUM IS NOT PRESENT.

ACTIVASE\* should be reconstituted by aseptically adding the appropriate volume of the accompanying Sterile Water for Injection, USP to the vial. It is important that ACTIVASE\* be reconstituted only with Sterile Water for Injection, USP without preservatives. Do not use Bacteriostatic Water for Injection, USP The reconstituted preparation results in a colorless to pale yellow transparent solution containing ACTIVASE\* 1.0 mg/mL at approximately pH 7.3. The osmolality of this solution is approximately 215 molegy(s).

5 mOsm/kg.

Because ACTIVASE® contains no antibacterial preservatives, it should be reconstituted immediately because ACTIVASE\* contains no antiquacterial preservatives, it should be reconstituted immediately before use. The solution may be used for intravenous administration within 8 hours following reconstitution when stored between 2-30°C. Before further dilution or administration, the product should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

ACTIVASE\* is stable for up to 8 hours in these solutions at room temperature. Exposure to light has

o effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, e.g., Sterie Water for Injection, USP or preservative-containing solutions for further dilution. No other medication should be added to infusion solutions containing ACTIVASE\* Any unused infusion solution should be discarded.

HOW SUPPLIED: ACTIVASE\* is supplied as a sterile, lyophilized powder in 20 mg and 50 mg vials containing avaruum each packaged with dilugat for reconstitution.

containing vacuum, each packaged with diluent for reconstitution.

Storage Store lyophilized ACTIVASE® at controlled room temperature not to exceed 30°C (86°F), or under refrigeration (2-8°C/36-46°F). Protect the lyophilized material during extended storage from excessive exposure to light.

Do not use beyond the expiration date stamped on the vial.

ACTIVASE® Alteplase, recombinant

GENENTECH® INC.

460 Point San Bruno Blvd. South San Francisco, CA 94080

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	Total Dose ≤ 100 mg	Total Dose > 100 mg
gastrointestinal	5%	5%
genitourinary	4%	4%
ecchymosis	1%	<1%
retroperitoneal	<1%	<1%
epistaxis	<1%	<1%
gingival	<1%	<1%

#### Genentech, Inc.

519 Inotropic Response to Dobutamine in Elderly Patients with **Decompensated Congestive Heart Failure** Michael W. Rich and Michael Imburgia 521 Long-Term Efficacy and Safety of Coenzyme Q<sub>10</sub> Therapy for **Idiopathic Dilated Cardiomyopathy** Per H. Langsjoen, Peter H. Langsjoen, and Karl Folkers Prevalence of Significant Congenital Heart Defects in Children of Parents with Fallot's Tetralogy Thomas M. Zellers, David J. Driscoll, and Virginia V. Michels Depressed Left Ventricular Systolic Ejection Force in Hypothyroidism Richard T. Lee, Maureen Plappert, and Martin G. St. John Sutton 527 False-Negative Diagnosis of Proximal Aortic Dissection by **Computed Tomography or Angiography and Possible Explanations Based on Transesophageal Echocardiographic Findings** Andreas Mügge, Werner G. Daniel, Joachim Laas, Reinhard Grote, and Paul R. Lichtlen 529

Right Ventricular Myocardial Mass Quantification with **Magnetic Resonance Imaging** 

Edward S. Mackey, Martin P. Sandler, Robert M. Campbell, Thomas P. Graham, Jr., James B. Atkinson, Ronald Price, and Gordon A. Moreau



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## FAST SEDATION AND



## EXCELLENT AMNESIA GO HAND IN HAND

#### Fast onset of sedation

- In Gastroscopy
- In Cardiac Catheterization/Angiography
- In Cystoscopy
- In Bronchoscopy

### Prompt recovery with few adverse reactions

Short elimination half-life

#### Excellent amnesia

PERCENTAGE OF PATIENTS WITH NO RECALL OF PROCEDURE<sup>1</sup>

NO RECALL OF SCOPE INTRODUCTION

71.3%

NO RECALL OF SCOPE WITHDRAWAL

82.3%

VERSED I.V. (midazolam HCI/Roche)

Especially valuable when repeat procedures may be required

#### Less irritation and phlebitis

Only 1.29% (2/155) incidence of phlebitis one week postprocedure with VERSED versus 7.63% (9/118) with diazepam.<sup>2</sup>

#### **Dosing Considerations**

Because serious and life-threatening cardiorespiratory adverse events have been reported with VERSED, provide for monitoring, detection and correction of these reactions for every patient regardless of age or health status.

As a standard precaution, prior to I.V. administration, oxygen and resuscitative equipment should be immediately available and personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation should be ensured.

For conscious sedation, VERSED should be titrated slowly; never give as a bolus. Respiratory depression and/or arrest may result from excess doses or rapid or single bolus. VERSED is 3 to 4 times as potent per mg as diazepam. Refer to the complete dosage and administration guidelines.

It is recommended that patients not drive or operate hazardous machinery after receiving VERSED until the effects of the drug (e.g., drowsiness) are gone or until the day after anesthesia. Decision must be individualized.

VERSED® Midazolam HCI/Roche © INSTEAD of diazepam

Please see summary of product information on adjacent page.

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The 1 mg/mL strength is recommended for I.V. conscious sedation.

References: 1. Roche Scientific Summary: The Evaluation of VERSED® (brand of midazolam HCI/Roche) (P., Roche Laboratories, a division of Hoffmann-La Roche Inc., 1 Jersey, 1986. 2. Phaosawasdi K, Rice P:SGA Journal 1987; Spring: 176-178.

VERSED® rand of midazolam HCI/Roche) (N

escribing, please consult complete product information, a summary of which follows:

Intravenous VERSED has been associated with respiratory depression and respi-Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, when this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)

The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzo-diazepines are contraindicated in patients with acute narrow angle glaucoma; may ed in open angle glaucoma only if patients are receiving appropriate therapy be used in open angle glaucoma only if patients are receiving appropriate therapy. 
WARNINGS: Never use without individualization of dosage. Prior to IV use in 
any dose, ensure immediate availability of oxygen, resuscitative equipment 
and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which 
can lead to hypoxia/cardiac arrest unless effective countermeasures are taken 
immediately. Vital signs should continue to be monitored during the recovery period. Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. For conscious sedation, do not administer IV by rapid or single bolus. Serious cardiorespiratory adverse events have These have included respiratory depression, apnea, respiratory arrest occurred. These have included respiratory depression, apried, respiratory ariest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic. Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding. Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary of anestnesia, premedicated or not. Patients with chronic bostructive purificially disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances. Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recom-mended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anes thesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malforma with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: General: Decrease intravenous doses in elderly and debilitated

patients. These patients will also probably take longer to recover completely after VERSED does not protect against increased intracranial pressure or against the heart

rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform

your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing.

Drug interactions: The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (e.g., morphine, meperidine, fentanyl) and also secobarbital

#### VERSED® (brand of midazolam HCI/Roche) INJECTION

and Innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, expect or duration of a single intulation does not succinylcholine. dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and etacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with

clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was Carcinogenesis, intragenesis, iniparment of retrility. Midazolari maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness in children below the age of 18 years have not

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV and 10.8% of patients following IV and 10.8% of patients following IV and 10.8% of patients following IV and patients following IV and IV IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: Respiratory: Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. Cardiovascular: Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. Gastrointestinal: Acid taste, excessive salivation, retching. CNS/Neuromuscular: Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, ness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. Special Sense: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. Integumentary: Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. Miscellaneous: Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma. Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midrazolam sugness that its abuse optionial is at least equiv. dependence potential of midazolam suggest that its abuse potential is at least equivnt to that of diazepam.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (e.g., sedation, somolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be

DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information. ection in the complete product information



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#### CASE REPORT

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**Atrial Standstill After Treadmill Exercise Test and Unique** Response to Isoproterenol Infusion in Recurrent Postexercise **Syncope** 

Yusuke Tamura, Osamu Onodera, Kunio Kodera, Yutaka Igarashi, Takashi Miida, Yoshifusa Aizawa, Tohru Izumi, Akira Shibata, and Satoshi Takano

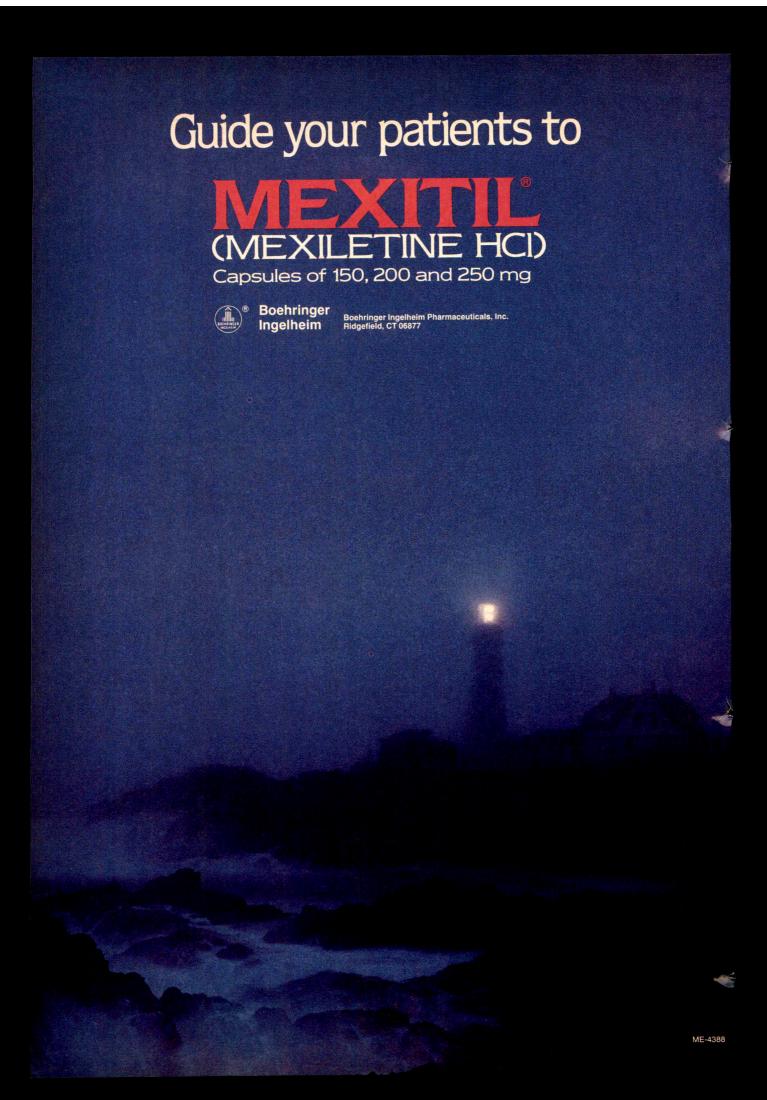
#### FROM THE EDITOR

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**Limited Research Funds and Cardiac Medicine Without Cardiac Surgery** 

William C. Roberts

**INSTRUCTIONS TO AUTHORS on page 538** 



The American Journal Cardiology

#### **Very Early Thrombolytic Therapy in Suspected Acute Myocardial Infarction**

The Thrombolysis Early in Acute Heart Attack Trial Study Group\*

Three hundred fifty-two patients with suspected acute myocardial infarction (AMI) were randomized to placebo (175) or tissue-type plasminogen activator (rt-PA) (177). Patients were eligible if evaluated within 165 minutes from onset of chest pain and if age was <75 years. Electrocardiographic criteria were not required. A mobile coronary care unit with a cardiologist present was used to initiate treatment at home in 29% of the patients. Primary endpoints were infarct size (serum lactate dehydrogenase isoenzyme<sub>1</sub> activity), left ventricular function (radioangiography) and exercise capacity at 30 days. AMI was diagnosed in 59% of all randomized patients. The incidence was similar in the 2 groups (placebo, 108, rt-PA, 101). Among all randomized patients, rt-PA was associated with significantly decreased infarct size and an increased ejection fraction. Among rt-PA-treated patients there were significantly fewer Q-wave infarctions. No difference in exercise capacity could be detected. No benefit was found in subgroups of patients without ST-segment elevation on the initial electrocardiogram. There were 18 (10.3%) and 11 (6.2%) deaths (p = 0.23) within 30 days in the placebo and rt-PA groups, respectively. Adverse reactions were similar in both groups with no excess of complications in the home-treated group. Very early treatment with rt-PA in patients with a strong suspicion of AMI and ST-segment elevation limits infarct size and improves left ventricular function. The infarct pattern is shifted from Q-wave to non-Q-wave infarcts by rt-PA. The study suggests that thrombolysis can be given before hospital admission without additional risk. Furthermore, electrocardiographic records are useful for selection of patients.

(Am J Cardiol 1990;65:401-407)

From the Division of Cardiology, Department of Medicine I, Sahlgrenska Hospital, S-413 45 Göteborg, Sweden. This study was supported by grants from Boehringer Ingelheim Zentrale GmbH, Ingelheim am Rhein, Germany, and from Arbetsmarknadens Försäkringsaktiebolag, Sweden. Manuscript received July 5, 1989; revised manuscript received October 13, 1989, and accepted October 14.

Address for reprints: Stig Holmberg, MD, the Division of Cardiology, Department of Medicine I, Sahlgrenska Hospital, S-413 45 Göteborg, Sweden. \*See Appendix.

he value of thrombolytic therapy in acute myocardial infarction (AMI) is well documented, with beneficial effects found on reperfusion, infarct size, left ventricular function and survival.1-8 It also seems that thrombolytic treatment is most effective when started soon after onset of AMI,<sup>5,7</sup> although this has not been shown in all studies.8 These observations have led investigators to search for new ways to reduce the delay from onset of symptoms to beginning of therapy. Initiation of treatment at home or in a mobile coronary care unit is 1 approach to reducing that delay. 9,10

The present study examined thrombolytic therapy very early after the onset of infarct symptoms. Patients were treated within 3 hours of symptom onset after evaluation by an experienced cardiologist in the home or hospital.

The primary aim of the study was to assess the effects of early thrombolysis by tissue-type plasminogen activator (rt-PA) compared to placebo on estimated infarct size, left ventricular function and exercise capacity at 30 days. A secondary aim was to assess mortality at 30 days. In addition, the feasibility and safety of very early treatment outside of the hospital were evaluated.

#### **METHODS**

Study population: The study was performed in Göteborg, Sweden, a city of 440,000 inhabitants, from October 1986 to April 1988. All inhabitants with suspected AMI were treated in 2 major hospitals. Patients eligible for inclusion in the study were identified either when they entered the hospital emergency room or when they called for an ambulance. A single mobile coronary care system serves the entire city, making prehospital treatment feasible. A cardiologist accompanied the ambulance when AMI was suspected. Inclusion criteria were age <75 years and pain highly suggestive of AMI with a duration of >15 minutes and <165 minutes at time of evaluation. Electrocardiographic criteria were not used to determine eligibility. Exclusion criteria included inability to give informed consent and obvious contraindications to thrombolytic therapy.

Regimen: Patients were randomized to receive either 100 mg rt-PA or placebo in a double-blind fashion as an intravenous infusion over 3 hours. Before start of infusion 5,000 IU of heparin was given intravenously. A second infusion of identical trial medication was given to patients with a second episode of severe chest pain.

**TABLE I** Baseline Characteristics of All Randomized Patients

TABLE I Baseline characteris	7000 017 111 711		a cionito
	Placebo	rt-PA	
1. 大学的 医皮肤	(n = 175)	(n = 177)	p Value
Age (yrs)			
Mean	62	62	
Median	63	64	
Female sex (%)	22	26	
Previous history (%)			
Myocardial infarction	33	39	
Angina pectoris	49	50	
Systemic hypertension	30	27	
Cardiac failure	9	8	
Diabetes mellitus	10	7	
Receiving $\beta$ blockers	41	37	
Receiving calcium antagonists	12	20	0.06
Receiving long-acting nitrates	17	21	
Clinical status			
Hypotension (<90 mm Hg) (%)	3	4	
Rales present (%)	22	25	
Systolic BP (mean mm Hg)	144	141	
Diastolic BP (mean mm Hg)	90*	84*	0.004
Heart rate (mean beats/min)	73 <sup>†</sup>	74 <sup>†</sup>	
Interval from onset of pain to			
start of infusion			
Mean (min)	111	107	
Median (min)	111	103	
Prehospital entry (%)	24	33	0.07
ST elevation at entry (%)	60	54	
Metoprolol IV at entry (%)	61	65	

BP = blood pressure; IV = intravenous; rt-PA = tissue-type plasminogen activator.
\* Five and 3 patients missing, respectively; † 1 and 6 patients missing, respectively.

After completion of trial infusion a heparin infusion was started and oral anticoagulant treatment was given. When therapeutic plasma concentration of dicumarol was achieved (international ratio 2.24 to 4.01) heparin was discontinued. Oral anticoagulant treatment was maintained for 30 days. Acetylsalicylic acid was given to all patients in a dosage of 125 mg daily starting at the time of completion of the trial medication infusion and continued for 1 year. All patients without contraindication to  $\beta$  blockade were given metoprolol 15 mg intravenously immediately after start of trial medication followed by 200 mg orally for at least 1 year.

Measures: Blood samples for creatine kinase were collected every 4 hours during the first 24 hours and for serum aspartate aminotransferase every 24 hours during the first 72 hours. These enzymes were used for the diagnosis of AMI. For infarct size determination serum lactate dehydrogenase isoenzyme<sub>1</sub> was measured every 12 hours during the first 72 hours. The maximal value was taken as an indication of infarct size. Serum aspartate aminotransferase was determined according to the Scandinavian Committee on Enzymes.<sup>11</sup> Serum creatine kinase was determined according to a modified recommendation by the Scandinavian Committee on Enzymes,12 and serum lactate dehydrogenase isoenzyme<sub>1</sub> according to an isoimmune method.<sup>13</sup> The upper normal range for aspartate aminotransferase, creatine kinase and serum lactate dehydrogenase isoenzyme, were 0.7 \(\mu\)kat/liter, 3.3 \(\mu\)kat/liter and 3.0 \(\mu\)kat/liter, respectively (1  $\mu$ kat = 60 IU/liter).

Within a few minutes after start of trial medication a 12-lead electrocardiogram was taken in both prehospi-

TABLE II Maximum Serum Lactate Dehydrogenase
Isoenzyme: Activity and Ejection Fraction\*

isoenzyme Activity and Ejection	Traction		2000
	Placebo	rt-PA	p Value
Lactate dehydrogenase			
isoenzyme <sub>1</sub> (μkat/liter)			
All pts (159/160)	13.3	9.0	0.001
ST elevation at entry (96/86)	19.6	13.2	0.001
No ST elevation at entry (63/74)	3.7	4.1	
Ejection fraction			
All pts (142/153)	0.55	0.59	0.01
ST elevation at entry (86/87)	0.49	0.55	0.005
No ST elevation at entry (56/66)	0.63	0.64	
* Values are mean. rt-PA = tissue-type plasminogen activator.	47.4		

tal and hospital patients. The electrocardiogram was repeated after 50 minutes, 210 minutes, and on day 4 and on day 30.

At 30 days patients had exercise stress testing and resting radionuclide ventriculography as outpatients. The exercise stress test was performed on a bicycle ergometer starting at 30 watts with a stepwise increase of workload of 10 watts/min. The stress test was discontinued for severe angina, fatigue, claudication or arrhythmias. In patients with signs of exercise-induced myocardial ischemia (ST-segment depression ≥2 mm in precordial leads or ≥1 mm in extremity leads) coronary angiography was performed to determine if revascularization was needed. Resting left ventricular ejection fraction was assessed using equilibrium radionuclide angiocardiography.

During the study period of 30 days, angioplasty or coronary artery bypass surgery was performed only if clinically significant postinfarction angina occurred.

**Statistical analysis:** Sample size was calculated for 2 of the primary endpoints: infarct size and left ventricular function.

Based on peak serum lactate dehydrogenase isoenzyme<sub>1</sub> values, we assumed that the average AMI size would be reduced 25%. To demonstrate this difference in infarct size between the placebo and rt-PA group with a p <0.05 (2-sided) and a power of 80% would require 2 × 105 patients with AMI. We calculated that 50% of the included patients would actually develop an AMI and thus a total of 420 patients were needed.

We assumed that left ventricular function as determined by radionuclide angiography for global measures would be better preserved in the treated group than in the placebo group. We estimated that global ejection fraction measured at 30 days would be  $0.40 \pm 0.14$  in the placebo group and  $0.45 \pm 0.14$  in the rt-PA group. To demonstrate this difference with a p <0.05 and a power of 80%, 2 × 123 patients with AMI, and thus a total of 492 patients, would be required.

The comparisons between groups were performed by Fisher's permutation test.<sup>14</sup> That test includes Fisher's exact test for comparison of proportions. Nominal p values, uncorrected for multiple comparisons, are given. Two-sided tests were used.

**Organization:** The study was approved by the Ethics Committee of the University of Göteborg. An indepen-

dent Safety and Data Monitoring Committee continuously monitored mortality and severe complications, such as major bleeding and life-threatening arrhythmias. An International Advisory Board had the responsibility for reviewing the trial protocol and to make ethical and scientific policy decisions.

#### RESULTS

The study started in October 1986. In April 1988 the Advisory Board recommended that randomization be halted, with new studies suggesting placebo-controlled trials were no longer justifiable. The study was stopped prematurely in April 1988 after randomizing 352 patients.

Baseline characteristics: A total of 479 patients met inclusion criteria and were evaluated for participation. Of these, 127 were excluded by physical examination, history and other criteria. A total of 352 patients were randomized to treatment with placebo (175) or rt-PA (177). Baseline characteristics (Table I) were similar in the 2 groups, except for a slightly higher use of calcium antagonists and lower diastolic blood pressure in the rt-PA group. The mean time between onset of pain and start of blind infusion was 111 and 107 minutes for placebo and rt-PA groups, respectively.

Elevation of the ST-segment on the initial electrocardiogram was present in 200 of the randomized patients at entry. In 88% of these patients, a definite AMI developed during the first 3 days. Most of the patients without AMI were diagnosed as having ischemic heart disease. A total of 152 patients did not have ST-segment elevation at entry; the ST-segment was either normal or depressed, or other changes that obscured STsegment elevation were present (e.g., bundle branch block). In this subset of patients, 21% developed a definite AMI. Most of the patients without ST-segment elevation subsequently were diagnosed as having angina pectoris (53%), with 9% having a noncardiac disorder.

In 251 patients the start of trial medication took place after arrival at the hospital, while in 101 patients

treatment was started at home (29%). Among patients with treatment initiated in the hospital, 67% developed a definite initial AMI. Among patients treated outside the hospital, 42% developed a definite AMI. The mean difference in start of treatment between the prehospital (83.0 minutes) and the hospital (119.3 minutes) patients was 36 minutes.

Serum lactate dehydrogenase isoenzyme<sub>1</sub> activity: Data for serum lactate dehydrogenase isoenzyme<sub>1</sub> activity were obtained in 319 of the 352 randomized patients. Data were missing because of early deaths in 7 placebo and 5 rt-PA patients and for technical reasons in 9 and 12 patients, respectively. The maximal serum lactate dehydrogenase isoenzyme, activity was significantly lower in the rt-PA group than in the placebo group (mean values 9.0 vs 13.3 µkat/liter) (median values 5.3 vs 8.2; p <0.01) (when p values regarding primary endpoints were corrected for multiple comparisons according to Bonferroni correction, p = 0.004) (Table II). This difference was significantly (for interaction, p = 0.03) more emphasized in patients with ST-segment elevation at entry. A similar difference was obtained among all patients for maximum creatinine kinase between rt-PA and placebo-treated patients (17.3 vs 22.4  $\mu$ kat/liter; p = 0.06), despite the recognition that this measure is known to be further elevated with effective thrombolysis. The cumulative distribution of maximal serum lactate dehydrogenase isoenzyme<sub>1</sub> activity in all patients is shown in Figure 1. These curves suggest an effect of rt-PA in patients with small and medium-sized infarctions.

**Ejection fraction:** Resting global left ventricular ejection fraction assessed by radionuclide angiocardiography at 30 days was available in 295 of the 352 randomized patients. The major reason that ventriculograms were not obtained was death before 30 days (18 placebo, 11 rt-PA patients). Data from a further 15 placebo and 13 rt-PA patients were missing mainly because of physical inability and unwillingness. Among randomized and assessable patients the ejection fraction

FIGURE 1. Cumulative distributions of infarct size determined from maximum serum lactate dehydrogenase isoenzyme<sub>1</sub> (LD<sub>1</sub>) activity in placebo patients (broken line) and in patients allocated to thrombolysis (solid line). Patients who died before completion of the measurements are not included. rt-PA = tissuetype plasminogen activator.

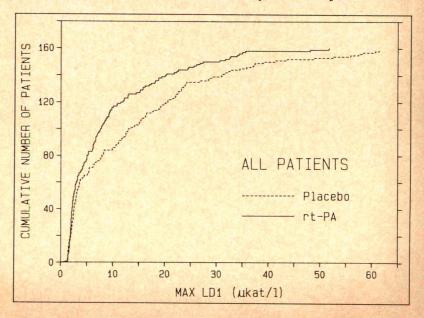


TABLE III Thirty-Day Mortality, Mode of Death and Death Within 24 Hours All Patients ST Elevation No ST Elevation rt-PA Placebo rt-PA rt-PA Placebo Placebo (n = 177)(n = 105)(n = 95)(n = 70)(n = 82)(n = 175)15 5 3 6 18 11 Total deaths (n) Cardiac deaths (n) 3 7(5) 1(1) 2(2) 2(1) Cardiac failure 2 1(1) 1(1) 2 3 Sudden death 4 4(1) 0 0 0 Cardiac rupture 2 3(1) 0 0 3 Reinfarction 0 0 0 At bypass surgery 0 0 0 At surgery for aortic dissection (n) 1 0 1(1) 0 0 0 Unknown (n) Figures within parentheses refer to deaths within 24 hours (9 placebo vs 5 rt-PA) rt-PA = tissue-type plasminogen activator.

was significantly higher among those who had received rt-PA than those in the placebo group (0.59 vs 0.55; p <0.05, after Bonferonni correction, p = 0.04) (Table II). The difference in left ventricular ejection fraction was only seen among patients with initial ST-segment elevation. The cumulative distributions of ejection fraction in all patients are shown in Figure 2.

Exercise capacity: An exercise bicycle stress test was performed approximately 30 days after randomization in 286 patients. The reasons for not performing a stress test were death (18 placebo, 11 rt-PA), emotional or physical inability (9 placebo, 6 rt-PA), unwillingness (7 placebo, 5 rt-PA), unstable angina requiring angiography (2 placebo, 3 rt-PA), bypass surgery (1 placebo, 1 rt-PA) and noncardiac diagnosis (1 placebo, 2 rt-PA). No differences in exercise capacity between the 2 treatment groups were detected. The reasons for terminating the bicycle tests were similar in patients receiving rt-PA and placebo with fatigue as the dominating cause. The criteria for subsequent investigation with coronary angiography were fulfilled among 18% of the patients in the placebo group and 23% in the rt-PA group, respectively.

Mortality: As listed in Table III, there were 18 deaths in the placebo group (10.3%), compared to 11

deaths in the rt-PA group (6.2%), a nonsignificant reduction of 40%.

Autopsy was performed in 20 cases. Most of the patients died from congestive heart failure. There were 4 deaths due to rupture of the ventricular wall, all in the placebo group. Fatal reinfarction was seen in 2 of the patients in the placebo group and in 3 of the patients in the rt-PA group. A dissecting aortic aneurysm was diagnosed in 1 patient in the placebo group and this patient died on day 3 in connection with aortic surgery.

Nonfatal cardiac events: As shown in Figure 3, the development of confirmed AMI during the first 3 days in the hospital was similar in the 2 groups. The occurrence of Q-wave infarcts was lower and the occurrence of non-Q-wave infarcts was increased in the rt-PA group as compared with the placebo group.

The number of patients who received a second infusion was small, as was the number of patients with confirmed reinfarctions (Table IV). There were no differences between placebo- and rt-PA-treated patients. Angina pectoris was significantly more common among patients treated with rt-PA than among those treated with placebo. The frequency of ventricular fibrillation and cardiogenic shock during hospitalization was simi-

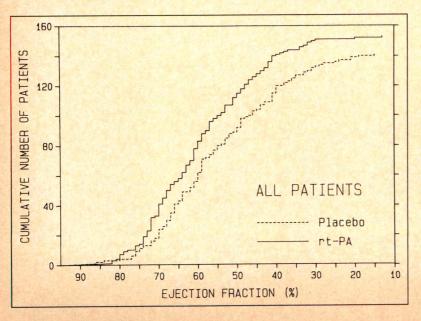


FIGURE 2. Cumulative distributions of ejection fraction as determined by radio-nuclide ventriculography at 30 days in placebo patients (broken line) and in patients allocated to thrombolysis (solid line). Abbreviation as in Figure 1.

TABLE IV Symptoms and Non-Fatal Cardiac Events Within 30 Days of Randomization (n) ST Elevation No ST Elevation **All Patients** Placebo rt-PA Placebo rt-PA Placebo rt-PA p Value p Value (n = 105)(n = 95)(n = 70)(n = 82)(n = 175)(n = 177)p Value 10 11 16 27 16 Readmission to CCU (n) 26 2 Reinfusion due to suspected reinfarction 5 5 3 2 8 6 6 3 2 3 Late infarction 6 2 Ventricular fibrillation 6 8 3 4 Cardiogenic shock 0 0 Coronary angioplasty 0 Coronary artery surgery 24 40 0.12 0.02 31 0.18 Angina pectoris 48 71 24 11 60 37 0.02 Cardiac failure 71 54 0.06

lar in the 2 groups. Cardiac failure before discharge, at 30-day follow-up, or both, tended to be more common among placebo than among rt-PA patients, and this difference among patients with ST-segment elevation was significant.

**Complications:** Gastrointestinal bleeding or hematuria was reported in 24 patients, 19 treated with rt-PA and 5 patients treated with placebo. No cerebral hemorrhages were seen and only 3 patients, all treated with placebo, required blood transfusions. No other adverse events and bleeding complications occurred. No allergic reactions were seen. Hypotension during infusion (systolic blood pressure <90 mm Hg) was most common in the rt-PA group (27 vs 19 patients; p >0.25) and hypotension requiring pressors was observed in 10 rt-PA patients versus 6 placebo patients (p >0.25).

Shortening of delay time: For all patients whose treatment was started before hospitalization the time was recorded for each step in the procedure until the patient entered the coronary care unit. From these data it could be calculated that the infusion of trial medication would have started on average 40 minutes later if the patient instead had been transported to the hospital and included in the study in-hospital.

#### DISCUSSION

CCU = coronary care unit

The demonstrated beneficial effects of rt-PA concerning infarct size and left ventricular function are in agreement with larger thrombolytic trials. 15-17 However, this study differs in some aspects from most other studies. First, the study was performed in a city where virtually all AMI patients were transported to and treated in the 2 participating hospitals. Therefore, the patient series could be regarded as representative for AMI in the community eligible for early thrombolysis. Second, a maximal effort was made to start treatment as early as possible. Two approaches were taken to achieve this goal. A mobile coronary care unit with a cardiologist present was used and when possible treatment was initiated at home in the prehospital period. Furthermore, no electrocardiographic criteria were required for randomization, assuming that myocardial necrosis could be prevented in patients treated in the very early phase of the AMI process before they had developed typical electrocardiographic changes. Third, the study was designed to defer all invasive procedures until

after 30 days in all cases except those with repetitive ischemic attacks. This approach tested the ability of a smaller hospital to give patients thrombolytic therapy without immediate access to more aggressive procedures (e.g., angioplasty). Finally, the  $\beta$ -blocker metoprolol was given intravenously at the start of administration of trial medication in 66% of all patients, followed by oral metoprolol during the study period.

Conventionally, thrombolysis is started in-hospital. However, in several small studies treatment has been started outside the hospital with an estimated shortening of delay time of 30 to 60 minutes. 9,18 A limitation of infarct size, especially in anterior wall infarction, in comparison to hospital treatment, has been reported. 10,18 In our study of 101 patients treated in the prehospital phase the shortening of delay time was 40 minutes. Even with a fairly complicated protocol including administration of heparin, trial medication and  $\beta$ blockers, this approach was feasible. Due to the relatively small number of patients in this trial and the small number developing AMI, whether rt-PA infusion is more effective when started before arrival at the hospital compared to when given after arrival remains questionable. The important conclusion regarding the prehospital treatment is that the study suggests that thera-

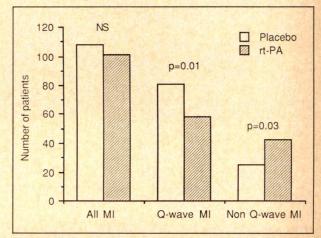


FIGURE 3. The total number of definite acute myocardial infarction (MI) in the placebo and the tissue-type plasminogen activator (rt-PA) groups, and the distribution of Q-wave and non-Q-wave infarctions in the 2 treatment groups. NS = difference not significant.

py could be started earlier without additional risk for the patient.

In most studies, only patients with signs of ST-segment elevation on the electrocardiogram have been treated. In this study, electrocardiographic criteria were not used to potentially help patients very early in the process leading to AMI. It has been observed that many patients with AMI have experienced a period of hours or days with accelerating angina and that such patients have intracoronary thrombi that can be dissolved by thrombolytic therapy. 19-21 If these patients could be identified and thrombolysis started very early, it should be hypothetically possible to prevent AMI. However, there was no evidence in our study to support this hypothesis, because about the same number of patients developed a definite AMI in both treatment groups (108 placebo vs 101 rt-PA; difference not significant). Whether there are favorable effects of thrombolytic therapy in unstable angina still remains to be demonstrated and requires different experimental protocols than those used in the present study.

Previous studies have shown that approximately 35 to 40% of patients with myocardial infarction never demonstrate ST-segment elevation.<sup>22</sup> These patients tend to develop non-Q-wave infarctions. If they are to receive the benefit of thrombolytic therapy it is necessary to include them irrespective of electrocardiographic changes. This was done in the ISIS-2<sup>7</sup> and the ASSET<sup>6</sup> trials. In both these trials the fatality rate was very low in the patients with normal electrocardiograms at entry. A significant reduction in mortality in this subgroup was reported for ISIS-2, while a trend in the same direction was seen in ASSET.

However, even if the ISIS-2 study was able to demonstrate reduction in mortality for those without ST-segment elevation, the mortality was very low both in the treated and in the placebo groups. It is debatable whether this group of patients should be exposed to the risks of thrombolytic therapy for the small (although significant) gain in mortality. More important is that within the group selected for thrombolytic therapy on the clinical suspicion of AMI but without initial ST-segment elevation, only a small proportion, in our study 21%, developed an infarct. Thus, 79% are exposed to the risk of thrombolysis without any benefit. This is a strong argument against routine treatment with thrombolysis in patients without ST-segment elevation.

There was a significant shift in infarct pattern with more Q-wave infarcts in the placebo group and more non-Q-wave infarcts in the rt-PA group. This is consistent with the reduction in infarct size and indicates that some subendocardial infarcts did not progress to transmural infarcts.

Earlier studies have claimed a very high reocclusion rate after thrombolysis, which has resulted in studies on the value of early invasive interventions such as angioplasty. <sup>23–25</sup> This study was designed to elucidate the feasibility of deferring all invasive procedures during the first month except in patients with repeated severe ischemic attacks. This design corresponds to the approach

in a typical smaller hospital where coronary arteriography support is limited or nonexistent. Reocclusion was diagnosed from clinical signs. Coronary arteriography was only performed when indicated by symptoms. We found no clinical signs of increased reocclusion rate in the rt-PA group. A confirmed reinfarction occurred only in 6 patients in the placebo group and in 3 in the rt-PA group. Among patients who developed an AMI, coronary angioplasty was necessary in 1 from the rt-PA group and bypass surgery was performed acutely in 1 placebo-treated patient.

The treatment with acetylsalicylic acid and  $\beta$  blockade might have been an important factor for the low rate of reocclusions during the first month, since these drugs have been shown to reduce reinfarction rates. 7,26 Because our patient sample could be regarded as highly representative for a whole AMI population, our data strongly suggest that thrombolysis could be performed in almost any hospital without a significant number of patients requiring emergency invasive procedures.

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#### **APPENDIX**

#### Participants in the Thrombolysis Early in Acute Heart Attack Trial Study

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Safety and data monitoring committee: John Kjekshus, MD, Anders Odén, PhD.

Advisory board: Ed Varnauskas, MD, Desmond Julian, MD, Jacobus Lubsen, MD, John Lennane, MD, Lars Wilhelmsen, MD, Stig Holmberg, MD, Anders Odén, PhD.

# The Independence of Cycle Length Variability and Exercise Testing on Predicting Mortality of Patients Surviving Acute Myocardial Infarction

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Cycle length variability (CLV), defined as the standard deviation of normal cycle length intervals, has been found to be a powerful predictor of subsequent mortality in a population of 808 survivors of acute myocardial infarction. Decreased CLV is associated with a significant increase in mortality. **CLV** remained an independent predictor of outcome even after adjusting for left ventricular ejection fraction, clinical risk factors, heart rate and ventricular arrhythmias. In the same population of survivors of acute myocardial infarction, the results of exercise testing also strongly predicted outcome, with those failing to take the test having the worst survival, and those completing the low-level stress test taken before discharge having the best prognosis. The hypothesis that the status of stress test (completed; did not complete; failed to take) and **CLV** were measuring the same factor related to mortality was tested. Although the distribution of CLV was shifted to higher CLV in patients who completed the test and to lower CLV in those who failed to take the test, both predictors of mortality remained independent predictors of long-term mortality (average of 31 months of follow-up) after controlling for each other. Moreover, subgroups with an approximate 15-fold difference in mortality were defined using both variables (CLV <50 ms, did not take test had a 54% mortality; CLV >100 ms, completed the test had a mortality of 3.5%). CLV is a measure of autonomic tone; it is not strongly related to exercise ability and using the results of both stress testing and CLV results in the identification of subgroups of postinfarction patients with markedly disparate risks of mortality.

ycle length variability, defined as the standard deviation of the normal cycles found on the 24hour ambulatory electrocardiogram recorded in postmyocardial infarction patients before discharge, is a potent univariate predictor of long-term mortality, and continues to be an independent predictor even after controlling for heart rate, ectopic ventricular activity, ejection fraction and clinical features such as heart failure and presence of rales. We have referred to this variable as heart rate variability.1 However, since this term has also been used to define the standard deviation of heart rate itself rather than the standard deviation of the normal cycle length intervals, we have changed our terminology to the more specific cardiac cycle length variability (CLV). The mechanism for this relation is not known. One hypothesis has been that decreased CLV reflects decreased vagal tone, increased sympathetic tone, or both. Altered autonomic tone has been demonstrated to increase the prevalence of malignant ventricular arrhythmias in experimental models.2-5 It also occurs with diabetic neuropathy, a condition associated with increased sudden death.6 Another explanation is that decreased CLV represents a response to diminished exercise tolerance; for example, the patient who is severely limited will remain essentially inactive and thus have limited heart rate changes during the day: indeed, we have shown that stratifying patients by exercise performance (categorized to those completing a low-level exercise test, failing to complete and not taking the test) was a powerful predictor of 1-year mortality.

In our original report, CLV was shown to be related to factors predictive of mortality, including duration of exercise, ventricular premature complex rate, number of ventricular premature complex pairs or number of all repetitive ventricular premature complexes, the last 3 obtained from the 24-hour Holter recording. The purpose of this analysis was to establish whether CLV measured on the 24-hour Holter monitor was a predictor of mortality independent of exercise test parameters. To test the hypothesis whether CLV and the results of exercise testing were independent predictors of mortality or were measuring the same adverse risk factor, we compared the predictive value of CLV with those parameters of exercise testing reflecting heart rate and blood pressure response that we previously had found to be predictors of poor survival.7

METHODS

Population: Patients from 9 hospitals located in New York, New York, Rochester, New York, St. Louis,

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\*See Appendix.

TABLE I Relation of CLV and Exercise Test Parameters on Mortality

	<50	50–100	>100	Overall
Exercise test performance				
Completed	9 (3/32)	9 (19/223)	4 (4/114)	7 (26/369)
Incomplete	30 (13/43)	16 (24/148)	13 (8/60)	18 (45/251)
No test	54 (27/50)	22 (22/101)	19 (7/37)	30 (56/188)
Maximum HR (beats/min)				
<120	13 (7/52)	10 (29/277)	7 (10/142)	10 (46/471)
≥120	39 (9/23)	14 (13/92)	6 (2/35)	16 (24/150)
Change in HR (beats/min)				
<30	21 (6/29)	10 (11/108)	10 (4/41)	12 (21/178)
30-40	17 (4/23)	10 (11/105)	8 (4/51)	11 (19/179)
>40	26 (6/23)	13 (20/156)	5 (4/85)	11 (30/264)
Maximum BP (mm Hg)				
<120	30 (7/23)	9 (9/96)	11 (3/28)	13 (19/147)
>120	18 (9/50)	11 (30/265)	6 (9/14)	15 (48/329)
Change in BP (mm Hg)		作品 化乙烷烷 克达		
<10	25 (6/24)	17 (18/109)	10 (4/42)	14 (28/175)
10-25	18 (4/22)	9 (9/105)	8 (4/49)	10 (17/176)
>25	23 (6/26)	8 (12/145)	4 (3/84)	8 (21/255)

Missouri, and Tucson, Arizona, were enrolled in this study. Patients younger than 70 years who survived the coronary care unit phase of acute myocardial infarction were eligible for enrollment. The definition of acute myocardial infarction and the procedures for enrollment, data acquisition and follow-up have been published.<sup>8,9</sup> Of the 867 patients who enrolled, 820 had Holter recordings. Twelve of the 820 patients who had recordings were excluded because of atrial fibrillation, implanted cardiac pacemaker or battery failure in the last portion of the tape, leaving 808 patients with valid estimates of CLV; these patients are the subject of this report.

Of the patients with valid measurement of CLV, 620 had low-level exercise tests; of these, 369 completed the test and 251 began the test but failed to complete it. The treadmill protocol has been described previously. The grade was 0% for 3 minutes, 5% for the next 3 minutes and 10% for the final 3 minutes. After 1 minute at 1 mph the speed was increased to 1.7 mph for the final 8 minutes. The final 3 minutes were identical to stage I of the Bruce protocol. The duration of the test was thus 9 minutes, but it was terminated early if the patient felt uncomfortable and wished to stop, if there was any decrease in blood pressure, if there was ST-segment depression of 4 mm or if the heart rate exceeded 150 beats/min. Blood pressure was recorded at 1-minute intervals with a standard arm cuff.

**Primary risk variables:** Two-channel, 24-hour ambulatory electrocardiographic recordings were done just before discharge, after patients were ambulatory, and were analyzed by computer with manual overread. 11-13 CLV was calculated in the following manner. The arrhythmia analysis algorithms used by the computer system gave a label to each detected QRS complex. Cycles in which beats had normal morphologic characteristics and whose cycle lengths were within 20% duration of the preceding cycle length were measured. A technician was given an opportunity to review portions of the com-

puter-processed Holter electrocardiograms and to modify any of the computer labels applied. In particular, periods with the highest and the lowest average RR intervals were always reviewed. After human overreading, the annotated QRS by QRS data stream was processed by another computer program, which computed the average RR interval of normal cycles and the standard deviation of the RR intervals around the average cycle length that was then the CLV index.

Mortality data: One hundred twenty-seven of the 808 patients we analyzed died on or before December 31, 1982. For the present report all-cause mortality is used as the endpoint. We also analyzed the data using 1-year mortality and survival time as outcome variables. Because all of the analyses showed essentially the same results, we have chosen all-cause mortality for reasons of simplicity. We also examined cause-specific mortality, in particular sudden death, as an outcome. The numbers were small and no differences were seen.

Statistical analysis: Categorical models using allcause mortality as the dependent variable, CLV and various exercise testing parameters were constructed and fit with the Statistical Analysis System CATMOD procedure, using the maximum likelihood estimates of parameters and significance. 14 CLV was categorized as <50 ms, 50 to 100 ms and >100 ms, as in our prior report. Based on our prior analyses, 5 parameters of the exercise test were chosen: (1) overall status of the test, categorized as to whether the full 9-minute protocol was completed, whether the test was attempted but not completed or whether the test was not attempted (for any reason); (2) among those attempting the test, whether their heart rate increased to at least 120 beats/ min; (3) whether the change in heart rate over baseline was <30 beats/min, 30 to 40 beats/min or >40 beats/ min; (4) whether the systolic blood pressure increased to at least 120 mm Hg; and (5) whether the change in blood pressure over baseline was <10 mm Hg, 10 to 25 mm Hg or >25 mm Hg.

TABLE II Statistical Tests of Independence of CLV and Exercise Test Parameters

CLV		CLV Factor			Fit		Association	
Factor	Chi-square	p Value	Chi-square	p Value	Chi-square	p Value	Chi-square	p Value
Performance*	22.91	0.0001	33.03	0.0001	4.63	0.33	33.70	0.0001
Maximum HR <sup>†</sup>	9.60	0.01	3.37	0.07	3.61	0.17	3.70	0.16
Change in HR*	10.56	0.005	0.20	0.90	2.12	0.71	8.47	0.08
Maximum BP†	10.88	0.004	0.26	0.61	2.12	0.35	10.54	0.005
Change in BP*	11.37	0.003	5.57	0.06	1.91	0.75	4.68	0.32

<sup>\*</sup> Chi-square for each factor is 2 degrees of freedom, for fit of the model (interaction) 4 degrees of freedom and for association 4 degrees of freedom.

\*Chi-square for each factor is 1 degree of freedom, for fit of the model (interaction) 2 degrees of freedom and for association 2 degrees of freedom.

\*Abbraviations as in Table 1. Abbreviations as in Table I.

#### RESULTS

Table I lists the mortality in the 9 subgroups formed by the exercise test status classification and CLV (Figure 1). There is more than a 15-fold gradient of mortality. Twenty-seven of 50 patients with CLV <50 ms who did not take the exercise test died during follow-up (54%) whereas only 3.5% (4 of 114) of those patients who completed the test and had CLV >100 ms died during follow-up. As in Table I, there is an association between CLV and exercise test parameters, e.g., only 9% (32 of 369) of those completing the exercise test had CLV <50 ms, while 17% (43 of 251) of those with incomplete tests and 27% (50 of 188) of those with no test had CLV <50 ms. As in Table II, CLV was associated with exercise performance status and maximum blood pressure during the exercise test. The categorical model demonstrated significant, independent effects of both exercise test performance (chi-square = 33.03, p <0.0001) and CLV (chi-square = 22.91, p <0.0001). There was no significant interaction between the variables, as determined by the fit of the main effects only model (chi-square = 4.63, p = 0.33). At any exercise test classification, CLV <50 ms was associated with an increase in mortality, whereas those with CLV >100 ms had lower mortality. Table II also lists statistical tests of association between each of the exercise test parameters and CLV.

We had previously found that in those patients who took the exercise test, heart rate and blood pressure response predicted 1-year mortality. As in Table I, even when controlling for blood pressure or heart rate (either as above a threshold or as a change measure) patients with CLV <50 ms were consistently at higher risk. As in Table II, the association of CLV with mortality remained significant in each model.

#### DISCUSSION

We have previously demonstrated that both the status of exercise testing and CLV predict mortality in survivors of acute myocardial infarction, and that in the group who took the exercise test certain blood pressure and heart rate responses predicted mortality. One criticism of CLV as a measure predicting mortality is that it may reflect only the level of activity of the patient recovering from an acute myocardial infarction. Thus, it is postulated that sicker or more inactive people with very limited activity would show less heart rate variability and that CLV only measures this activity status. An analysis of the components responsible for heart rate variability in those with high and low CLVs militates against this simple hypothesis. 15 We have found that 1 major component responsible for CLV is slowing of heart rate during sleep. In patients with low CLV, nocturnal slowing is severely attenuated. This cannot rea-

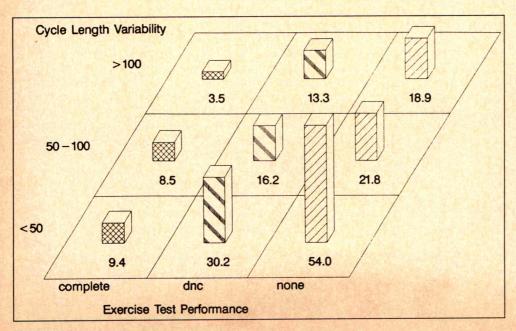


FIGURE 1. The heights of the bars represent the total mortality in each of the 9 groups and show the relative independence of each feature. Complete = completed the 9-minute protocol; dnc = attempted the exercise protocol, but did not complete it; None = did not take the exercise test.

sonably be attributed to difference in activity level. Another major difference between the low CLV and high CLV groups is a marked reduction of cycle interval changes >50 ms in the low CLV group. These interval changes are again more frequently seen in sleep recordings but occur both at rest and during activity. Furthermore, if level of activity were the major determinant of CLV, one would expect a close relation between results of early exercise testing and of CLV determination and no independent effect on mortality. This is clearly not borne out by our data. For any exercise status result, a low CLV was associated with an increase in mortality. Indeed, using these 2 safe and easily obtained noninvasive tests, subgroups of survivors of acute myocardial infarction with mortalities ranging from 4% (completed exercise test, CLV >100 ms) to 54% (did not take exercise test, CLV <50 ms) could be defined.

Furthermore, those variables previously found to be associated with an adverse mortality effect on exercise testing (maximum heart rate >120 beats/min, maximum blood pressure <120 mm Hg) only showed this adverse association in the group with CLV <50. The groups with CLV >50 and maximum heart rate >120 beats/min or maximum blood pressure <120 mm Hg showed essentially no difference in mortality from those groups with maximum blood pressure >120 mm Hg or maximum heart rate <120 beats/min. Additionally, we have shown that the exercise testing retains its usefulness when the patient is taking  $\beta$ -blocking drugs. <sup>16</sup> Thus, CLV was measuring some autonomic influence, not merely reflecting a level of conditioning that exercise testing does, and CLV is an important predictor of mortality irrespective of exercise performance or response to standardized exercise challenge. Using 2 easily measured, safe, noninvasive procedures, subgroups of patients surviving infarctions with a 15-fold difference in long-term mortality can be identified. In addition, since CLV and exercise testing are independent predictors of mortality it seems unlikely that the factors that exercise testing measures, such as ischemia, condition in the traditional sense and general physical condition, are the responsible factors for increased mortality that CLV is measuring. There is now strong circumstantial evidence that CLV is measuring relative autonomic balance and that patients with low CLV have decreased vagal and increased sympathetic tone predisposing to sudden death. Further work to delineate better the individual determinants of this simple measure of autonomic function is needed.

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#### **APPENDIX**

#### **Study Participants**

Multicenter Postinfarction Research Group Executive Committee: Arthur J. Moss, MD, Chairman; J. Thomas Bigger, Jr., MD, Robert B. Case, MD, John Gillespie, MD, Robert E. Goldstein, MD, Henry M. Greenberg, MD, Ronald Krone, MD, Frank I. Marcus, MD, Charles L. Odoroff, PhD, and G. Charles Oliver, MD.

Mortality Committee: Frank I. Marcus, MD (chairman); Leonard Cobb, MD, Jesse Edwards MD, and Lewis Kuller,

Biostatistics Committee: Charles L. Odoroff, PhD (chairman); Henry T. Davis, PhD, Joseph L. Fleiss, PhD, and J. Philip Miller.

Enrolling Hospitals: The Presbyterian Hospital, Roosevelt Hospital, and St. Luke's Hospital Center, New York, New York; Highland Hospital, Rochester, New York; The Jewish Hospital and St. Luke's Hospital, St. Louis, Missouri; and University of Arizona Health Science Center, Tucson Medical Center, and St. Joseph's Hospital, Tucson, Arizona.

### Ventricular Ectopic Activity During Myocardial Ischemic Episodes in Ambulatory Patients

Shlomo Stern, MD, Shmuel Banai, MD, Andre Keren, MD, and Dan Tzivoni, MD

The association between ventricular ectopic activity (VEA) and ischemic episodes during everyday activities was investigated in ambulatory patients with stable angina pectoris. Seventy-five consecutive patients with proven coronary artery disease, ischemic episodes on Holter monitoring and positive treadmill tests, but without known ventricular arrhythmias, were prospectively studied. In these 75 patients, a total of 719 ischemic episodes were recorded during 127 twenty-four-hour monitoring periods. Forty-three patients had either no or only very low baseline VEA (<14 ventricular premature complexes [VPCs]/24 hours); none of these patients had increased VEA during any ischemic episode. However, among 32 patients who had ≥14 VPCs/24 hours (average 243 VPCs/24 hours), increased VEA during ischemic episodes was observed in 11 (31%). These 11 patients had a total of 174 ischemic episodes and the increased VEA appeared in 47 (27%) of the episodes. During 40 of the ischemic episodes the number of single VPCs increased significantly compared to the baseline background VEA: during 4 episodes trigeminy appeared and during another 3 bigeminy was observed. More complex VEA was not observed. Among the 11 patients with increased VEA, only 4 developed VPCs during treadmill testing. No correlation was found between the severity of the ischemic episodes (degree of ST depression and duration of ischemia) and the increased VEA. In 83% of these episodes the increased VEA appeared during the last (possibly reperfusion) phase. No correlation was found between the appearance of ventricular arrhythmias during ischemic episodes and the presence or absence of chest pain at the same time.

Thus, in about 33% of chronic stable angina patients without previously known ventricular arrhythmias but with a low-level "background" ectopic activity, increased VEA during ischemic episodes was identified by Holter monitoring, but no malignant ventricular arrhythmias were observed.

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The high prevalence of ventricular arrhythmias in patients with acute transmural ischemia or infarction has been the subject of several investigations. An association between transient ischemic episodes during normal daily activity and ventricular arrhythmias, however, is not well established. This possible association may be especially important because ischemic episodes during daily activity are more common in patients with coronary artery disease than previously assumed. Furthermore, the patient is frequently unaware of such transient ischemic episodes, as it has been shown that more than 66% of them are "silent." 5,6

In this study we investigated the relation between ischemic episodes during daily activities and the incidence of ventricular arrhythmias in a well-defined group of 75 consecutive patients with chronic coronary artery disease who neither exhibited baseline complex ventricular arrhythmias nor received antiarrhythmic therapy.

#### **METHODS**

Of the 1,250 patients referred to our service for Holter monitoring during a 6-month period in 1988, those who met the following criteria were included in this prospectively conducted study: (1) coronary artery disease, diagnosed on the basis of previous myocardial infarction or pathologic coronary arteriogram or typical exertional angina; (2) referral for Holter monitoring for ischemia evaluation; (3) ≥1 ischemic episode during a 24-hour Holter monitoring; and (4) a positive Bruce protocol treadmill test. Excluded were patients with acute myocardial infarction <6 months before the study, patients with known ventricular arrhythmias or those receiving antiarrhythmic therapy, patients with conduction disturbances, congestive heart failure, unstable angina during the last 3 months before the Holter monitoring and patients with an abnormal ST segment on the resting electrocardiogram that made the ST-segment analysis unreliable.

These criteria were met by 75 patients: 64 men and 11 women. The mean age was  $62 \pm 10$  years, 32 patients were in Canadian Heart Association class 0 to I, 35 patients in class II, 8 in class III and none in class IV. Fifteen patients (20%) had a previous myocardial infarction

Ambulatory Holter monitoring: Ambulatory Holter monitoring was performed while the patients were engaged in usual daily activities. A total of 127 twenty-four-hour monitoring periods were recorded and analyzed in this study. The mean monitoring period was 46 ± 29 hours/patient (range 24 to 192). Reel-to-reel 2-channel recorders (Applied Cardiac Systems, Inc.) were used; the gain of the recorders was adjusted to give 10

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mm for 1 mV. Silver-silver chloride skin electrodes were attached to the V<sub>3</sub>-like and V<sub>5</sub>-like positions.<sup>7</sup> The recorders were equipped with an event button and the patients were instructed to activate this button whenever they experienced symptoms of chest pain or discomfort. The tapes were analyzed on the CardioData Prodigy System using a computerized interactive analysis method.

Arrhythmia analysis: The following electrocardiographic abnormalities were automatically frozen, displayed and counted: heart rate >120 beats/min or <50 beats/min and all atrial or ventricular premature complexes (VPCs) or more complex types of arrhythmias.

ST analysis: ST analysis was performed on both channels by the following method: any deviation detected from the isoelectric PR interval and from the patient's baseline ST segment (elevation or depression, upsloping or downsloping) was displayed on the ST trend. Electrocardiographic samples were automatically printed out in real time 2 minutes before the ST depression, at onset of ischemia (1-mm ST depression), at time of maximal ST depression and maximal heart rate and on return of the depressed ST segment toward the isoelectric line. All printouts were verified by a physician. An ischemic episode was diagnosed if in at least 1 of the channels, ST-segment depression of ≥1 mm was detected at 60 ms after the J point, lasting for ≥60 seconds, and if after the episode, a full return of the ST segment to the isoelectric line was seen. All ST-deviation episodes were printed out as an "ST episode table" (Figure 1).

Association between ventricular arrhythmias and ischemic episodes: This association was established according to the expanded histogram print-out. This printout included, on the same time axis: heart rate histogram, 2-channel ST histogram and ventricular and supraventricular arrhythmia histograms (Figure 2). Each histogram display contained the information of 3 hours of recording. Verification of the association between ischemia and ventricular arrhythmia was done visually. The baseline background ventricular ectopic activity (VEA) was expressed as the mean number of VPCs ± the standard deviation in each monitoring day and the mean ± standard deviation of VPCs in each monitoring hour, excluding the ischemic periods (i.e., VPCs that appeared during an ischemic episode were not calculated as part of the background activity). In this way the day-to-day and hour-to-hour spontaneous variability of the background VEA was taken into account.

The number of VPCs during each ischemic episode was compared (1) to the number of VPCs during an immediately preceding, 5-times longer, nonischemic period; (2) to the number of VPCs during a mean, nonischemic period, of a similar duration; and (3) to the number of VPCs in the remaining, nonischemic part of the particular hour that contained the ischemic episode.

Increased VEA during an ischemic episode was diagnosed if all 3 following criteria were met: (1) the number of VPCs during the episode was at least 4 times greater than the number of VPCs during the preceding 5-times longer, nonischemic period; (2) the number of VPCs during the ischemic episode was greater than the mean number plus 3 standard deviations of VPCs during a nonischemic period of a similar duration; and (3) the number of VPCs during the ischemia was greater than the number of VPCs plus the standard deviation during the remaining nonischemic part of the hour.

The increased VEA was related to the different phases of the ischemic episodes; i.e., the early, peak and late (recovery) phases.

**Treadmill testing:** All patients performed a Bruce protocol treadmill stress test, and the VEA was measured during exercise and recovery periods.

Drug therapy during the Holter monitoring: The patients continued their usual antiischemic therapy during the monitoring day. This consisted of  $\beta$  blockers in 26 patients and calcium antagonists in 54. No patient received diuretics.

#### RESULTS

Ischemic episodes during Holter: The 75 patients had a total of 127 twenty-four-hour ambulatory Holter monitoring periods. During the 3,048 hours of recording, 719 ischemic episodes were detected, with a total duration of ischemia of 138 hours (4.5% of the time monitored); no episode with ST elevation was observed. The ischemia duration/patient/24 hours ranged from 2 to 413 minutes (mean  $63 \pm 62$  minutes/24 hours/patient) and the mean number of ischemic episodes/24 hours/patient was 5.7. Of the 719 ischemic episodes 589 were silent (82%) and 130 (18%) were associated with typical pain or definite chest discomfort.

Baseline ventricular ectopic activity: Of the 75 patients, 15 had no VPCs during their ambulatory moni-

<b>C</b> 11			tion thresh	ONSET	ONSET	MAX	MAX	MAX	HR at	shold: 1,0	
CH	ONSET	END	DURATION	HR	-2 HR	HR	ST ABS	DEA	MAX DEV	INTEGRAL	TYPI
1	10.52,9-1 1	0.55,9-1	0.03,0	99	88	99	-1,88	-1,38	98	3.08	
2	10.52,9-1 1	1.24,4-1	0.31,5	99 99 102	88	103 102 125 125	-1,38 -2,0 -3,75 -3,25	-2.34	98 101 101 120 120	3,08	
1	11.03,4-1 1	8 44 4-1	0.02,0	103	89 91	102	-2,0	-1,51 -3,2	101	74,36	I
2		8.49,4-1	0.46.5	105	96	125	-3.25	-3,66	120	91,91	
1	8.29.4-2	8.30,4-2	0.01,0	111	96 84	111 128 128	-1,88	-1,3 -3,74	111	1,17	
2		8.43,9-2	0.14,5	111	84 98	128	-3, 13	-3,74	128	16,97	
1	0.32,4-2	0.34,4-2	0.02,5	111	90	120	-3,63	-3,03	128	4,50	1
Su	mmory:		1.33,0		Elev	ation	: 0,0	0,0		227,60	

FIGURE 1. Printout of ST-depression episode table. ABS = absolute; CH = channel; DEV = deviation; HR = heart rate; MAX = maximal.

toring, 28 had <14 VPCs/24 hours, 32 had ≥14 VPCs/24 hours (mean number of VPCs/24 hours 243 ± 538, range 14 to 2,970); average 10.0 VPCs/hour. Five patients had ventricular couplets, with an average of 2/24 hours/patient; 1 patient had 1 episode of ventricular triplet; 10 patients had ventricular bigeminy or trigeminy, lasting an average of 10 minutes/24 hours/patient. More complex ventricular arrhythmias were not observed.

Increased ventricular ectopic activity during ischemic episodes: Increased VEA during ischemic episodes was not observed in any of the 15 patients without any baseline VPCs or in any of the 28 patients with <14 VPCs/24 hours. Increased VEA was observed only if ≥14 VPCs/24 hours were disclosed. Among the 32 such patients 11 (31%) had increased VEA (14.6% of the total of 75 patients). These 11 patients had a total of 174 ischemic episodes, with increased VEA in 47 (27%) (or 6.5% of the total of 719 episodes in the 75 patients). Of the 11 patients, 4 (36%) had previous myocardial infarctions, while among the 64 patients without VEA 11 (17%) had previous infarctions (difference not significant).

Therapy with  $\beta$  blockers did not seem to affect the incidence of increased VEA during ischemia, as 6 of the 11 patients with increased VEA were receiving  $\beta$ -blocker therapy while 20 of the 64 patients without VEA were receiving  $\beta$  blockers at the time of ambulatory monitoring (difference not significant). Of the 32 patients who had more than 14 VPCs/24 hours during the baseline (nonischemic) period, an increase in the fre-

quency of VPCs was observed in 11 patients (34.5%) during some of the ischemic periods, compared to the nonischemic periods. These 11 patients had a total of 174 ischemic episodes (mean  $7.17 \pm 2.9$  episodes/24 hours/patient) and the increased VEA was observed in 47 (27%) of these episodes.

During all 47 ischemic episodes diagnosed as having increased VEA, the frequency of VPCs was much higher than the expected spontaneous variability of the background activity (Figure 3). In 4 episodes new trigeminy and in 3 new bigeminy appeared. More complex ventricular arrhythmias were not observed. Figure 4 shows the relation between the number of ischemic episodes with and without increased VEA in the 11 patients.

Correlation between increased ventricular ectopic activity and degree of ischemia: No such correlation was found. The mean duration of an ischemic episode/ 24 hours was  $13.5 \pm 8.9$  minutes in the 64 patients without and  $13.3 \pm 10.2$  minutes in the 11 patients with increased VEA (difference not significant). Similarly, the ST-segment depression was not deeper in the group with increased VEA than in those patients without it  $(2.9 \pm 0.9 \text{ mm} \text{ and } 3.0 \pm 1.2 \text{ mm}, \text{ respectively; differ-}$ ence not significant). Furthermore, among the 11 patients with increased VEA, the mean duration of an ischemic episode with increased VEA was 13.3 minutes versus 14.0 minutes for the episodes without (difference not significant). The mean maximal ST depression was 2.4 mm in the episodes with increased VEA, compared to 3.0 mm in those without (difference not significant).

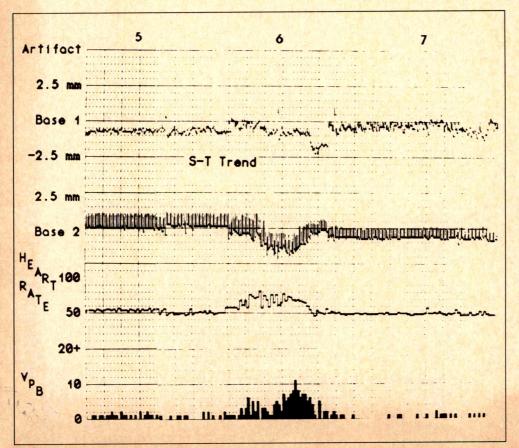


FIGURE 2. Four trend recordings: 2-channel ST trend, heart rate and ventricular ectopic activity. VPB = ventricular premature beat.

Time relation between increased ventricular ectopic activity and phase of ischemia: Of the 47 episodes with increased VEA, the increased VPC frequency was confined to the recovery phase, i.e., during return of the ST segment toward the isoelectric line in 38 (80.9%); it appeared at the peak ST depression phase in episodes (12.8%) and during the early phase of ischemia in 3 episodes (6.4%).

Relation between symptomatology of the patients and increased ventricular ectopic activity during ischemic episodes: Of the 11 patients with increased VEA, 7 had only silent ischemic episodes, while 4 had both symptomatic and silent episodes during monitoring. Of the 47 episodes with increased VEA, 39 were silent and 8 symptomatic. Thus, the ratio of 82% of silent episodes versus 18% of symptomatic episodes found in the total

of 719 episodes was also similar in the episodes with increased VEA (83 vs 17%, respectively).

Relation between increased ventricular ectopic activity on Holter and on treadmill testing: Among the 11 patients with increased VEA during ischemic episodes on Holter monitoring, only 4 patients showed VPCs during treadmill testing. Of these 4 patients, the VPCs appeared during the recovery phase in 3, and in 1 patient ventricular bigeminy was observed during the exercise period. This last patient had increased VEA in only 1 of 11 ischemic episodes on Holter.

#### **DISCUSSION**

Only a few previous studies investigated a possible association between transient subendocardial ischemia and increased VEA. Carboni et al<sup>8</sup> studied 32 patients

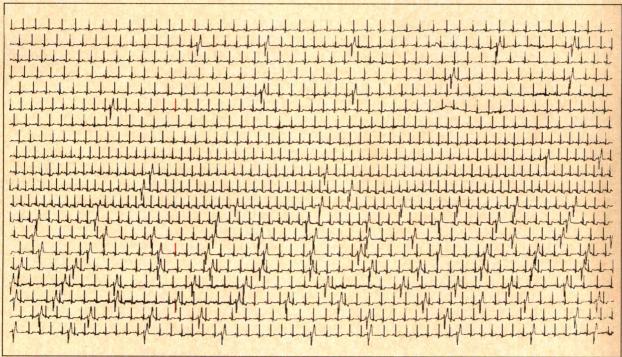
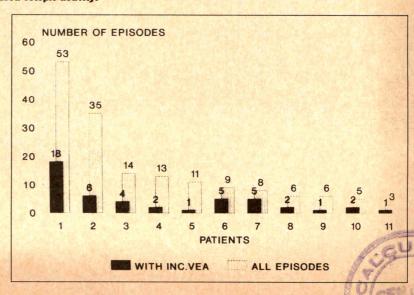


FIGURE 3. An ischemic episode, with increased ectopic activity.

FIGURE 4. Ischemic episodes with and without increased ventricular ectopic activity in 11 patients. INC. = increasing; VEA = ventricular ectopic activity.



with ischemic episodes during ambulatory monitoring: 11 (34%) had associated arrhythmias during the ischemic episodes. Of 115 episodes, 35% were associated with arrhythmias. This percent value is higher than that found in our investigation, and Carboni et al even found Lown grade 3 to 5 arrhythmias during ischemic episodes. It is not clear, however, whether these investigators excluded patients with known baseline ventricular arrhythmias from their study, as we did. Graboys et al<sup>9</sup> studied 20 patients with silent ischemic episodes during daily activities; only 1 patient had ventricular arrhythmias during ischemia, although altogether 15 patients exhibited VEA during the 24-hour monitoring period.

In our study, among 75 patients with ischemic episodes during daily activities, and no known ventricular arrhythmias before Holter monitoring, increased VEA during ischemic episodes was not observed unless the Holter monitoring disclosed a certain level of "background" VEA; this was found to be a VPC frequency of ≥14/24 hours. Of such patients 33% had increased VEA during ischemic episodes. This seems not to be due to a spontaneous variability in VPC frequency, as our 3 criteria for establishing this seem to be strict enough to avoid labeling normal hour-to-hour variability of background VPC as increased VEA.

In our study, the increased VEA appeared in 81% of the episodes during the last phase of the ischemia, when the ST segment already started to return toward the isoelectric line. This phase may be considered the "reperfusion period" of the ischemic episode. Carboni et al8 also observed the increased ectopic activity during the late phase of the episodes. "Reperfusion arrhythmias" are well recognized after transmural ischemia, <sup>10,11</sup> but appear to be less appreciated during the recovery from subendocardial ischemia. Our observations, supported by those of Carboni et al, suggest that these arrhythmias may also be present after transient subendocardial ischemia.

Bayes de Luna et al<sup>12</sup> found that patients with Prinzmetal's angina with >4-mm ST elevation or long attacks had more ventricular arrhythmias than those with <4-mm ST elevation or brief attacks. In other investigations no correlation was found between the duration of transient ST elevation and the appearance of VEA.<sup>13</sup> In our study the duration of subendocardial ischemia appeared not to be a factor in arrhythmogenesis, as the mean duration and the degree of ST depression of the episodes with increased VEA was not different from that of the episodes without.

Clinical implications: We investigated patients with chronic coronary artery disease without known ventricular ectopy and demonstrated increased VEA in 15% of them; the increased VEA was found in 6% of the ischemic episodes. These percentages became higher in the

population with a low-level "background" ectopic activity (≥14 VPCs/24 hours); in 31% of such patients and in 27% of their episodes, the ischemic episode was associated with increased VEA. Thus, although this phenomenon was disclosed only in a minority of the patients with chronic ischemic heart disease, in view of the high prevalence of this disease and the high frequency of ischemic episodes in such patients, the impact of increased ventricular ectopy may be quite substantial. The ventricular arrhythmias we found were not of the more complex types, but theoretically, any increase in VEA while part of the myocardium is ischemic might be a progenitor for more complex ventricular arrhythmias. A long-term follow-up of the patients with increased VEA may provide information concerning prognosis. Until such data are available, antiarrhythmic drug therapy in this population may not be warranted, but it seems clear that vigorous antiischemic therapy should be instituted.

Acknowledgment: We wish to express our gratitude to Noah Dodi and Vita Linda for devoted technical assistance.

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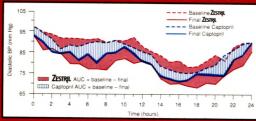
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# Usefulness of the Hyperventilation Test in Stable Exertional Angina Pectoris in Selecting Medical Therapy

Diego Ardissino, MD, Paolo Barberis, MD, Stefano De Servi, MD, Colomba Falcone, MD, Maurizio Ferrario, MD, Gloria Demicheli, MD, Paola Zanini, MD, Alberto Rolla, MD, Nicola Bruno, MD, Giuseppe Specchia, MD, and Carlo Montemartini, MD

To assess the prevalence of abnormal coronary vasoconstriction in stable exertional angina and to evaluate whether the presence of increased coronary tone may have therapeutic implications, we studied 83 consecutive patients with typical exertional angina, positive response to exercise stress testing and documented coronary artery disease. Abnormal coronary vasoconstriction was induced by a hyperventilation test in 16 patients (group I) while the remaining 67 had a negative response (group II). No differences were observed between the 2 groups with regard to clinical, exercise and angiographic data. All group I patients and 16 patients in group II repeated hyperventilation and exercise tests after the administration of dihydropyridine-type calcium antagonists (7 patients nifedipine, 9 patients felodipine). After treatment 15 of 16 group I patients had a negative response to the hyperventilation test. The total exercise duration was significantly increased (278  $\pm$  183 vs 554  $\pm$ 248 seconds; p <0.001) with higher values of rate pressure product at peak exercise (168  $\pm$  47 vs 235  $\pm$  67 mm Hg  $\times$  beats/min/100; p <0.0025). In group II no significant differences were observed between pre- and posttreatment values for total exercise duration (244  $\pm$  210 vs 308  $\pm$  243 seconds) and rate pressure product at peak exercise (170  $\pm$ 46 vs 188  $\pm$  56 mm Hg  $\times$  beats/min/100). These data show that the hyperventilation test can be used to select a subset of patients with stable exertional angina and detectable abnormal coronary vasoconstriction who will improve their exercise tolerance with coronary vasodilator treatment. (Am J Cardiol 1990;65:417-421)

t is well established that abnormal coronary vasoconstriction plays a major role in the pathogenesis of angina at rest1,2 and is the usual cause of myocardial ischemia in variant angina.3-6 Although stable exertional angina is classically attributed to increased myocardial oxygen consumption in the presence of fixed coronary lesions, it has been reported that changes in diameter of coronary stenoses could play an important role in modulating exercise tolerance.<sup>7-9</sup> The hyperventilation test has proved reliable and safe in detecting abnormal coronary vasoconstriction in patients with coronary artery disease. 10-15 The present study assesses the prevalence of abnormal coronary vasoconstriction detected by hyperventilation testing in patients with stable exertional angina and evaluates whether the detection of increased coronary tone may have therapeutic implications.

#### **METHODS**

Patient selection: Eighty-three consecutive patients admitted to our hospital from December 1985 to November 1988 formed the study group. The following 3 characteristics were required: history of typical chest pain induced by exercise or usual daily activity lasting ≥3 months; positive exercise stress testing, defined as the occurrence of ST-segment elevation or depression >1 mm measured 0.08 second after the J point, with or without chest pain; and angiographically documented coronary artery disease, defined as the presence of a >50% narrowing of one or more coronary arteries. None of the patients had episodes of angina at rest. Patients with severe hypertension, congestive heart failure, previous coronary artery bypass surgery, valvular heart disease and those receiving digitalis, diuretics or antiarrhythmic agents were excluded. Informed consent was obtained from each patient before the study.

**Study protocol:** Hyperventilation and exercise stress testing were performed between 9 and 12 A.M. in the fasting state and in pharmacologic wash-out. Beta-adrenergic blocking agents were gradually withdrawn at least 72 hours before the initiation of the study while nitrates and calcium antagonists were discontinued 24 hours before.

HYPERVENTILATION AND EXERCISE STRESS TESTING UNDER CONTROL CONDITIONS: Hyperventilation testing was performed by asking the patients to breathe as deeply and rapidly as possible (at least 30 respirations/min) for 5 minutes. A 12-lead electrocardiogram and blood pres-

Address for reprints: Diego Ardissino, MD, Divisione di Cardiologia, Policlinico S. Matteo, 27100 Pavia, Pavia, Italy.

From the Divisione di Cardiologia, IRCCS Policlinico S. Matteo, Universita' di Pavia, Pavia, Italy. Manuscript received April 17, 1989; revised manuscript received and accepted October 16, 1989.

**TABLE I** Clinical and Angiographic Characteristics of Patients with Positive (Group I) and Negative (Group II) Responses to the Hyperventilation Test

	Group I (n = 16)	Group II (n = 67)	p Value
Mean age (yrs)	57	54	NS
Sex: M/F	14/2	63/4	NS
Cigarette smokers (%)	10 (62)	31 (54)	NS
Previous AMI (%)	3 (19)	16 (28)	NS
Duration	12±9	$19 \pm 23$	NS
of angina (mos)			
Weekly episodes of	6±6	7 ± 5	NS
angina			
No. of coronary arteries na	arrowed >50%		
1 (%)	4 (25)	23 (34)	
2(%)	3 (19)	14 (21)	NS
3 (%)	9 (56)	30 (45)	
Ejection fraction (%)	62 ± 8	$56 \pm 16$	NS

**TABLE II** Rate Pressure Product Changes During Hyperventilation and Exercise Stress Testing

	Group I (n = 16)	Group II (n = 67)	p Value
Hyperventilation test	The Automotive		
Baseline	$91 \pm 21$	$94 \pm 27$	NS
Peak overbreathing	$121 \pm 35$	$135 \pm 43$	NS
Onset of ST changes	$107 \pm 38$	0	
Exercise test			
Baseline	$88 \pm 19$	$88 \pm 28$	NS
Onset of ST changes	$135 \pm 42$	142 ± 47	NS
Peak exercise	$168 \pm 47$	$165 \pm 43$	NS

Rate pressure product changes are BP × HR/100. BP = blood pressure (mm Hg); HR = heart rate (beats/min).

sure (cuff) were recorded at rest before starting overbreathing, every minute during the test and during the recovery phase for at least 10 minutes. An estimate of myocardial oxygen consumption was made from the rate-pressure product obtained by multiplying heart rate and systolic blood pressure (beats/min × systolic blood pressure/100). A positive hyperventilation test was signified by characteristic electrocardiographic changes (ST-segment elevation or depression ≥1 mm for 0.08 second after the J point), with or without chest pain, developing during the recovery phase of the test.<sup>15</sup>

Exercise testing was performed at least 2 hours after the end of the hyperventilation test with a multistage bicycle ergometer in the supine position with an initial workload of 25 watts and subsequent increases of 25 watts every 3 minutes. The test was stopped when moderate to severe angina or dyspnea or ST-segment depression ≥3 mm occurred. Standard 12-lead electrocardiogram and blood pressure were recorded before starting exercise, at 1-minute intervals during the test and for at least 10 minutes during the recovery phase. An estimate of myocardial oxygen consumption was also made from rate pressure product.

DRUG EVALUATION: In patients with a positive response to the hyperventilation test under control conditions, both hyperventilation and exercise tests were repeated the morning of the next day, 3 to 5 hours after the administration of dihydropyridine calcium antagonist drugs. The first 7 patients were pretreated with ni-

fedipine (20 mg orally) and the remaining 9 patients with felodipine (10 mg orally), a new calcium antagonist that is now under investigation in our institution. When a patient with a positive response to the hyperventilation test was enrolled for drug evaluation, the next patient with a negative response to the hyperventilation test under control conditions was evaluated after the same drug according to the study protocol.

Coronary arteriography: Coronary arteriography was performed using the Sones or Judkins technique after premedication with 10 mg of diazepam. When a significant lesion was noted the vessel was filmed again after sublingual nitroglycerin administration. Patients were classified as having 1-, 2- or 3-vessel disease according to the number of vessels with significant stenoses.

Statistical analysis: The Yates-corrected chi-square test was used to compare all the baseline characteristics between the 2 groups. The analysis of variance for ranked data was used to compare continuous variables. P <0.05 was considered statistically significant.

#### RESULTS

According to the hyperventilation test response the study population was divided in 2 groups. Group I comprised 16 patients who developed significant electrocardiographic changes during the recovery phase of the test, while the remaining 67 patients without electrocardiographic changes during recovery constitute group II.

Clinical and angiographic characteristics: There were no significant differences between group I and group II with regard to clinical characteristics including age, sex, history of smoking, duration of angina, mean weekly episodes of angina or prior myocardial infarction (Table I). The 2 groups were also similar with respect to the extent of coronary artery disease and ejection fraction.

Hyperventilation and exercise stress tests: Hyperventilation testing induced ST-segment depression in all patients of group I; precordial leads were involved in 12 patients and inferior or inferolateral leads in 4 patients. The electrocardiographic changes were accompanied by anginal pain in 12 patients. The onset of ST-segment depression occurred 161 ± 74 seconds after the end of overbreathing and the mean duration of the electrocardiographic changes was 144 ± 181 seconds with a maximum ST-segment shift of 1.8 ± 0.9 mm. The mean baseline rate pressure product increased during overbreathing while at the onset of ischemia it was approaching baseline values. In group II patients the mean rate pressure product also increased during overbreathing (Table II). No significant differences were observed between the 2 groups with regard to the rate pressure product changes during the hyperventilation test. A positive response to exercise stress testing associated with ST-segment depression was observed in all 83 patients. Anterior leads were involved in 11 (69%) patients in group I and in 39 (58%) patients in group II; inferior or inferolateral leads were involved in 5 (31%) patients in group I and in 28 (42%) in group II. Exercise-induced ST-segment changes were accompanied by chest pain in 13 (81%) group I patients and in 43 (64%) group II

patients. The mean exercise duration was  $278 \pm 185$  seconds in group I and  $244 \pm 210$  seconds in group II (difference not significant); the time to onset of ST-segment depression during exercise was  $194 \pm 113$  seconds in group I and  $166 \pm 141$  seconds in group II (difference not significant) with maximum ST-segment shift of  $1.9 \pm 1.2$  mm in group I and  $1.7 \pm 1.1$  mm in group II (difference not significant). The rate pressure product changes during the exercise test are listed in Table II. No significant differences were observed between the 2 groups with regard to exercise test results.

Hyperventilation and exercise stress testing after drug administration: After premedication with calcium antagonists, 15 of 16 patients in group I did not develop either chest pain or significant electrocardiographic changes during the hyperventilation test; only 1 patient continued to have a positive response to the test. The rate pressure product before starting hyperventilation and at peak overbreathing was comparable before and after treatment due to the fact that the drug-induced decrease in systolic blood pressure was compensated for by the simultaneous increase in heart rate (Table III). All patients except one continued to have a positive response to exercise stress testing. Total exercise duration, however, significantly increased after drug intake compared to control exercise (278 ± 183 vs 554 ± 248 seconds; p <0.001). The time to onset of electrocardiographic changes was also increased (194 ± 113 vs 414 ± 202 seconds; p <0.001) (Figure 1), while the degree of maximal ST-segment depression was similar before and after treatment. After drug intake the rate pressure product values before starting exercise were comparable to those observed under control conditions while at the onset of ST-segment depression and at peak exercise the mean values were significantly increased (Table III).

All 16 patients in group II who repeated the hyperventilation testing after calcium antagonists had a nega-

**TABLE III** Rate Pressure Product Changes During Hyperventilation and Exercise Stress Testing Before and After Drug Administration

	Group I (n = 16)		Group II (n = 16)	
	Pre	Post	Pre	Post
Hyperventilation test				
Baseline	91 ± 21	$95 \pm 20$	98 ± 21	81 ± 31
Peak overbreathing	$121 \pm 35$	$131 \pm 36$	151 ± 50	$161 \pm 57$
Onset of	$107 \pm 38$	0	0	0
ST changes				
Exercise test				
Baseline	$88 \pm 19$	$86 \pm 18$	$89 \pm 20$	82 ± 18
Onset of ST changes	$135 \pm 42$	207 ± 63*	$132 \pm 48$	149 ± 41
Peak exercise	$168 \pm 47$	$235 \pm 67^{\dagger}$	$170 \pm 46$	$188 \pm 56$

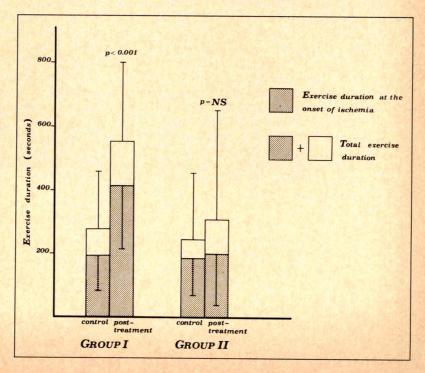
tive response. The rate pressure products at baseline and at peak of overbreathing before and after treatment were similar (Table III). After drug administration all patients had a positive response to exercise stress testing. No significant differences were observed between pre- and posttreatment values of total exercise duration (244  $\pm$  210 vs 308  $\pm$  243 seconds), time to onset of electrocardiographic changes (186  $\pm$  141 vs 199  $\pm$  167 seconds) (Figure 1) and maximum ST-segment depression. The rate pressure product at baseline, at the onset of electrocardiographic changes and at peak exercise was similar before and after treatment (Table III).

#### DISCUSSION

#### Role of coronary tone in stable exertional angina:

The concept that stable exertional angina is caused by increased myocardial oxygen consumption in the pres-

FIGURE 1. Total exercise duration (open columns + shaded columns) and time to the onset of ST-segment changes (shaded columns) under control conditions and after premedication with calcium antagonists in all group I patients and in 16 group II patients. In group I the total exercise duration and the time to onset of ST-segment changes significantly increased after drug intake compared to control exercise. No differences were observed between pre- and posttreatment values in group II. P values are for both total exercise duration and time to onset of ST-segment changes.



ence of fixed coronary lesions implies that myocardial ischemia reproducibly occurs at a given level of cardiac work. The spontaneous changes in anginal threshold experienced by many patients with classic stable angina and the pronounced day-to-day variability in the number of ischemic attacks during usual daily life seem to challenge this concept. The lack of reproducibility has been confirmed by Holter monitoring studies in which most of the ischemic attacks occurring out-of-hospital are not preceded by an excessive increase in heart rate and the heart rate at the onset of ischemia is variable and often significantly lower than that observed during exercise stress testing. 16-18 On the basis of these considerations the increase in myocardial oxygen demand may not necessarily be the only mechanism responsible for many episodes of transient ischemia occurring during normal daily activities. Epstein and Talbot19 developed the hypothesis that subtle alterations in coronary tone superimposed on an intrinsic coronary lesion can alter the maximal capacity of coronary flow delivery and thereby change angina threshold. They19 hypothesized that there is a spectrum of coronary tone in dynamic large vessels. When coronary tone is low, patients can perform heavy exercise because myocardial oxygen supply is impaired only by the presence of organic coronary stenosis. In contrast, when coronary tone is high, oxygen supply is primarily decreased and even moderate activities may induce chest pain and myocardial ischemia. Evidence supporting this hypothesis is provided by recent studies demonstrating that ergonovine, a drug known to constrict large epicardial vessels, may provoke coronary spasms in patients with stable exertional angina,20 and that a sizable proportion of patients with exertional angina can have ergonovine-induced transient myocardial ischemia.7

Significance of hyperventilation testing in stable exertional angina: A more physiologic vasoconstrictor stimulus, such as hyperventilation, has also been shown to provoke myocardial ischemia in patients with coronary artery disease. 10-14 We have recently reported that the ischemic ST-segment changes occurring during the recovery phase of the hyperventilation test are related to primary reduction in coronary blood flow.15 In the present study the hyperventilation test induced myocardial ischemia during the recovery phase in about 20% of patients with classic stable exertional angina and a positive response to exercise stress testing. Because the rate pressure product at the onset of ST-changes was comparable to the rate pressure product in basal conditions and far lower than the rate pressure product required to produce ischemia during exercise, it is reasonable to assume that a transient impairment of blood supplyrather than an increase in oxygen consumption—is the cause of hyperventilation-induced myocardial ischemia. The hyperventilation test results after the administration of calcium antagonists further supported this hypothesis. Nifedipine or felodipine, which are dihydropyridine-derivative drugs known to reduce coronary tone without affecting myocardial oxygen consumption, prevented hyperventilation-induced myocardial ischemia. Although the hyperventilation test appears to identify a subset of patients whose coronary tone is like-

ly to undergo dynamic changes, this does not necessarily imply that these changes may interfere with ischemic attacks on effort. The behavior of coronary tone during effort has been indirectly investigated by assessing exercise capacity before and after administration of calcium antagonists. In patients with a positive response to hyperventilation testing, the improvement in exercise capacity after nifedipine or felodipine was significantly greater than in patients with a negative hyperventilation test response. Different individual susceptibility of coronary stenoses in undergoing dynamic changes during exercise may explain why, among patients with similar exercise capacity and similar severity of coronary artery disease, only some had improved exercise tolerance with coronary vasodilatators.<sup>21</sup>

Limitations: One possible limitation of this study is that none of the patients had the hyperventilation test repeated after placebo administration; thus it is impossible to be certain that the change from a positive to a negative test result was due to therapy rather than to spontaneous variation in response to repeated testing. Moreover, the effects of calcium antagonists on exercise tolerance have been assessed in only a small subgroup of patients with a negative response to the hyperventilation test. Theoretically, exercise test results after premedication with calcium antagonists could have been different if all patients had been assessed. The lack of angiographic documentation during hyperventilation and exercise stress testing did not allow us to have direct proof of coronary vasoconstriction. Only indirect indexes, such as the rate pressure product at the onset of ischemia and the response to calcium antagonists, have been used to investigate the pathogenetic mechanism of ischemia. However, because of the curvilinear relation between caliber and resistance to flow, it is possible that small changes in lumen, particularly at the site of severe stenoses and probably undetected by visual inspection of the arteriograms, could provoke large modifications in coronary resistance and flow resulting in electrocardiographic signs of myocardial ischemia. In fact, Bertrand et al<sup>20</sup> after ergonovine, observed a change in coronary diameter in 4% of patients with exertional angina, while Crea et al7 found that the ergonovine test produced diagnostic ST-segment changes in 29% of patients with the same clinical characteristics.

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#### **Effect of Pretreatment with Aspirin Versus Aspirin Plus Dipyridamole on Frequency and Type of Acute Complications of Percutaneous Transluminal Coronary Angioplasty**

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It is unknown whether the addition of dipyridamole to aspirin as pretreatment for patients undergoing percutaneous transluminal coronary angioplasty (PTCA) decreases acute complications. In this study 232 patients were prospectively randomized to receive either aspirin 325 mg orally 3 times daily (group 1, n = 115) or aspirin 325 mg orally 3 times daily plus dipyridamole 75 mg orally 3 times daily (group 2, n = 117) before elective PTCA. All clinical, angiographic and PTCA-related variables were similar between groups. Angiographic success rate was 93% in both groups. Clinical success was achieved in 107 patients (92%) in group 1 and in 101 patients (88%) in group 2 (difference not significant). Q-wave myocardial infarction occurred in 2 patients (1.7%) in group 1 and 5 patients (4.3%)in group 2 (difference not significant). Emergency coronary artery bypass grafting was required in 3 patients (2.6%) in group 1 and 7 patients (6.1%) in group 2 (difference not significant). There was 1 inhospital death (in group 2). In this study, the addition of dipyridamole to aspirin as pretreatment of patients undergoing PTCA did not significantly reduce acute complications compared to aspirin

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yocardial infarction, emergency coronary artery bypass graft surgery and death have re-I mained the major acute complications after elective percutaneous transluminal coronary angioplasty (PTCA). Platelet aggregation and acute thrombosis are important factors in the genesis of these complications.2 Aspirin has been one of the standard antiplatelet agents for most patients undergoing PTCA. Dipyridamole has been shown to prevent platelet aggregation in animal models after injury to the vasculature and its mechanism of action is different from that of aspirin.3 This has prompted many angioplasty operators to add dipyridamole to aspirin empirically as pretreatment for patients undergoing PTCA.4-8 It has recently been shown that the combination of aspirin and dipyridamole reduces the incidence of in-hospital Q-wave myocardial infarctions after PTCA compared with placebo.9 It remains unknown whether dipyridamole has any additional benefit compared to aspirin alone. This study was performed to determine whether the addition of dipyridamole to aspirin decreases acute complications in patients undergoing PTCA.

#### **METHODS**

Patients: The study population consisted of 268 patients who underwent PTCA at our institution between February 1986 and January 1987. These patients represent a subset of a larger population recruited to determine the influence of varying doses of aspirin, dipyridamole, or both, on late restenosis after PTCA. Excluded from the study were patients who had an evolving myocardial infarction, a contraindication to high dose antiplatelet agents (e.g., recent gastrointestinal bleeding or allergy to either drug), PTCA to saphenous vein grafts or internal mammary arteries or unwillingness to participate in the study. All 268 patients gave written consent to participate in the study, which was approved by the Human Investigations Committee of Emory University Hospital. After consent was obtained, the physician opened a sealed envelope that contained the name and dose of the antiplatelet agent(s) to be assigned: aspirin 325 mg orally 3 times a day (group 1) or aspirin 325 mg orally 3 times a day plus dipyridamole 75 mg orally 3 times a day (group 2). These envelopes were furnished

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by the Department of Epidemiology and Biostatistics and assured equal distribution of both treatment arms. The physician then wrote for the assigned therapy in the patient's medical orders to be given as soon as possible. After careful chart review, it was found that 232 (87%) of the 268 patients received at least 1 dose of the assigned therapy before PTCA. A number of our elective PTCA patients were admitted the day of the procedure, and this resulted in a small number of patients not receiving their assigned antiplatelet therapy before PTCA. Of the 232 patients who received the assigned dose of antiplatelet therapy before PTCA, 117 were in group 1 and 115 were in group 2. The results will be presented based on the treatment received and not on the intention to treat.

Angioplasty technique: Procedures were performed using a standard technique. Patients were given 10,000 U of heparin at the start of the procedure and an additional 5,000 U every hour if the procedure time exceeded 1 hour. Intracoronary nitroglycerin (200  $\mu$ g) was administered before the lesion was crossed with the dilation catheter.

Data collection: Data were prospectively recorded by physicians on standard forms and entered into the Emory Cardiac Data Bank. Clinical data included patient age, sex, presence of unstable angina (defined as angina of increasing severity, including pain at rest or angina of new onset, i.e., within the past 2 months). In addition, the antiplatelet agents that the patient was taking before admission were also recorded. Angiographic data included extent and distribution of coronary artery disease (multivessel disease was defined as ≥50% diameter stenosis in ≥2 major epicardial vessels or a large branch thereof), vessel tortuosity (defined as a bend in the artery >45°), lesion shape (either eccentric or concentric), lesion calcification and lesion length (measured in millimeters in the least foreshortened view using digital calipers). In addition, the number of total occlusions and branch point stenosis were recorded. Procedural data included pre- and post-PTCA diameter stenosis measured as the mean of 2 orthogonal views using previously validated electronic digital calipers. 11,12 Pre- and post-PTCA pressure gradients were recorded when available. An intimal tear was defined as angiographic evidence of intimal damage within the length of the dilated lesion. A dissection was defined as an intimal tear extending beyond the length of the dilated lesion. In addition, the prolonged use of heparin after PTCA, which is not our usual routine, was recorded. Angiographic success was defined as a final diameter stenosis of <50%. Clinical success was defined as the achievement of angiographic success without the need for subsequent in-hospital emergency or elective coronary artery bypass grafting or the occurrence of myocardial infarction (presence of new O-waves ≥40 ms or creatine kinase ≥510 U with any MB fraction) or death. In-hospital complications included Q-wave myocardial infarction (defined as the appearance of new Q waves); emergency coronary surgery (defined as surgery performed on the same or subsequent days for unstable

**TABLE I** Clinical Characteristics Group 1 Group 2 (n = 117)(n = 115)p Value Age (yrs)  $59 \pm 10$  $58 \pm 10$ 0.47 Sex: M/F (%) 88 (75)/29 (25) 86 (75)/29 (25) 0.94 Unstable angina (%) 69 (76) 66 (82) 0.52 Antiplatelet agents before admission (%) None 72 (61) 67 (58) 0.61 ASA only 37 (32) 34 (30) 0.73 DIP only 3(3) 2(2) 0.66 ASA + DIP 5 (4) 12 (10) 0.07 Group 1 received ASA only; group 2 received ASA + DIP. ASA = aspirin; DIP = dipyridamole.

TABLE II Angiographic C	haracteristics		
	Group 1 (n = 117)	Group 2 (n = 115)	p Value
Coronary artery dilated (%)	MENTE LOUI	MAN AND	55 3 7 7 8
LAD	63 (54)	59 (51)	0.70
LC	32 (27)	32 (28)	0.94
Right	32 (27)	40 (35)	0.22
Multivessel CAD (%)	51 (44)	47 (41)	0.67
Tortuosity (%)	19 (16)	18 (16)	0.90
Eccentric lesion (%)	72 (62)	80 (70)	0.20
Narrowing calcified (%)	14 (12)	9 (8)	0.29
Length of narrowing (mm)	$9.4 \pm 5.7$	$9.8 \pm 6.3$	0.68
Total occlusions (%)	10 (9)	8 (7)	0.65
Branch point stenosis (%)	20 (17)	20 (17)	0.95
Thrombus (%)	5 (4)	6 (5)	0.74

Group 1 received ASA only; group 2 received ASA + DIP. CAD = coronary artery disease; LAD = left anterior descending coronary artery; LC = left circumflex artery; other abbreviations as in Table I.

	Group 1 (n = 117)	Group 2 (n = 115)	p Value
Angiographic success (%)	109 (93)	107 (93)	0.97
Clinical success (%)	107 (92)	107 (93)	0.36
Single lesion PTCA (%)	85 (73)	83 (72)	0.94
Multilesion PTCA (%)	32 (27)	32 (28)	0.94
Percent diameter stenosis	02 (27)	32 (20)	0.54
Pre-PTCA	$76 \pm 15$	75 ± 13	0.46
Post-PTCA	33 ± 19	$35 \pm 18$	0.50
Pressure gradients (mm Hg)			0.00
Pre-PTCA (n = 204)	$59 \pm 16$	62 ± 20	0.23
Post-PTCA (n = 175)	15±8	15±8	0.97
Intimal tear (%)	47 (40)	43 (37)	0.66
Dissection (%)	6 (5)	8(7)	0.56
Post-PTCA heparin (%)	56 (48)	51 (44)	0.59

Group 1 received ASA only; group 2 received ASA + DIP. PTCA = percutaneous transluminal coronary angioplasty; other abbreviations as in Table I.

or ongoing myocardial ischemia or because of the presence of severe intimal dissection or a severe residual lesion "threatening" imminent closure of the instrumented vessel during the same hospitalization); elective coronary surgery (defined as surgery performed in patients with angiographically unsuccessful PTCA who did not have ongoing myocardial ischemia or "threatening" anatomic signs during the same hospitalization); and death (defined as any death occurring during the hospitalization).

	Related to Randomization Treatment		Related to Preadmission Antiplatelet Therapy				
	Group 1 (n = 117)	Group 2 (n = 115)	p Value	None (n = 139)	ASA Only (n = 71)	DIP Only (n = 5)	ASA + DIF (n = 17)
Q-wave MI (%)	2 (1.7)	5 (4.3)	0.24	7 (5)	0	0	0
CABG (%)	3 (2.6)	7 (6.1)	0.19	7 (5)	3 (4.2)	0	0
Emergency	0	0	_	0	0	0	0
Elective Death (%)	0	1 (0.9)	0.31	1 (0.7)	0	0	0

Data analysis: Continuous variables are presented as mean ± 1 standard deviation and were analyzed by unpaired t tests. Categorical variables were compared by chi-square analysis or Fisher's exact test. A p value of <0.05 was considered significant.

#### RESULTS

Clinical: There were no differences in the clinical characteristics between patients in group 1 and group 2 with regard to patient age, sex, and presence of unstable angina (Table I). The antiplatelet therapy before admission for PTCA is listed in Table I. Seventy-two patients (61%) in group 1 and 67 patients (58%) in group 2 were not taking aspirin or dipyridamole before their hospital admission (difference not significant).

Angiographic: There were no differences in baseline angiographic characteristics (Table II).

Procedural: Angiographic success, clinical success, pre- and post-PTCA diameter stenosis, pre- and post-PTCA pressure gradients, post-PTCA intimal tears or dissections and use of heparin after the procedure were similar between groups (Table III).

Complications: Each complication was recorded separately per patient; for example, a patient having a Qwave myocardial infarction and coronary artery bypass graft surgery had the 2 complications listed separately (Table IV). Q-wave myocardial infarction occurred in 2 patients (1.7%) in group 1 and in 5 patients (4.3%) in group 2. Emergency coronary artery bypass graft surgery was performed in 3 patients (2.6%) in group 1 and 7 patients (6.1%) in group 2. In the patients requiring emergency coronary artery bypass graft surgery, Qwave myocardial infarction occurred in 0 of the 3 patients in group 1 and in 3 of the 7 patients in group 2. There were no patients in either group who required elective coronary artery bypass grafting. There were no deaths in group 1 and 1 death in a patient in group 2, who also had a Q-wave myocardial infarction and died 4 days after PTCA secondary to complications related to a mesenteric artery occlusion.

One hundred thirty-nine (60%) of the 232 study patients were not taking antiplatelet therapy before admission for PTCA (Table IV). This included 72 patients (61%) randomized to group 1 and 67 patients (58%) randomized to group 2. Q-wave myocardial infarction occurred in 2 patients (2.8%) in group 1 and in 5 patients (7.5%) in group 2 who were not taking antiplatelet therapy before admission. Emergency coronary artery bypass graft surgery was required in 1 patient (1.4%) in group 1 and 6 patients (8.9%) in group 2 (p =0.06) who were not taking antiplatelet therapy before admission.

#### DISCUSSION

In the 1985-1986 National Heart, Lung, and Blood Institute PTCA registry, in-hospital myocardial infarction, emergency surgery and death occurred in 5.5% of patients with 1-vessel disease, 7.8% of patients with 2vessel disease and 9.7% of patients with 3-vessel disease.1 Coronary dissection, platelet aggregation and acute thrombosis are important factors in determining acute complications after angioplasty. This has led many PTCA operators to pretreat patients undergoing PTCA with antiplatelet drugs such as aspirin and dipyridamole.

Aspirin is a nonsteroidal antiinflammatory agent, which potently and irreversibly inactivates platelet cyclooxygenase by acetylation. Although all of aspirin's antithrombotic effects have been attributed to this blockade of thromboxane A<sub>2</sub> formation by platelets, there is evidence for antithrombotic effects independent of its inactivation of cyclooxygenase. 13 Dipyridamole is a pyrimidopyrimidine derivative that is among the 50 most commonly prescribed drugs in the United States. The mechanism of action of dipyridamole as an antithrombotic drug in vivo is controversial. Three mechanisms have been suggested by which dipyridamole inhibits platelet function: (1) the inhibition of the phosphodiesterase enzyme in platelets, resulting in an increase in intraplatelet cyclic AMP and the consequent potentiation of the platelet-inhibiting actions of prostacyclin, (2) direct stimulation of the release of this eicosanoid by vascular endothelium or (3) inhibition of cellular uptake and metabolism of adenosine, thereby increasing its concentration at the platelet-vascular interface. In addition to such direct effects, dipyridamole may augment the platelet-inhibiting action of aspirin through a pharmacokinetic interaction.14

Although it may seem logical to combine aspirin and dipyridamole to inhibit thrombosis by different mechanisms of action, the evidence that orally administered dipyridamole exerts antithrombotic action in humans is very limited. In the majority of prospective clinical trials, dipyridamole was added to aspirin and compared to placebo rather than compared directly against aspirin. The few clinical trials in which aspirin alone has been compared with aspirin plus dipyridamole suggest that dipyridamole contributes little if anything to the anti-thrombotic action of aspirin in prevention of myocardial infarction, strokes, transient ischemic attacks or stenosis of saphenous vein grafts after coronary artery bypass surgery. 15-18

Barnathan et al<sup>19</sup> performed a retrospective analysis of 263 consecutive initially successful PTCA procedures. Patients were then classified into 3 groups based on the type and extent of antiplatelet therapy received. Group 1 (no aspirin) consisted of patients who did not receive aspirin either before admission or in the hospital before PTCA (with or without dipyridamole). Group 2 ("standard treatment") received aspirin with or without dipyridamole but did not receive both drugs before admission and in the hospital. Group 3 ("maximal treatment") received both aspirin and dipyridamole before admission and in the hospital before PTCA. They concluded that some aspirin is probably better than none and that long-term as well as short-term dipyridamole before the procedure may add additional benefit in terms of reducing the incidence of thrombus at the PTCA site, determined by a 30-minute post-PTCA angiogram. However, they suggested that prospective trials be performed to confirm their conclusions.

Schwartz et al<sup>9</sup> performed a prospective randomized study in which patients undergoing angioplasty either received aspirin plus dipyridamole (n = 189) or placebo (n = 187). In-hospital post-PTCA myocardial infarction occurred in 3 patients (1.6%) in the aspirin plus dipyridamole group and 13 patients (6.9%) in the placebo group (p = 0.011). They concluded that pretreatment of patients undergoing PTCA with aspirin plus dipyridamole reduces the incidence of Q-wave infarction during or early after PTCA. The question left unanswered by this study was whether dipyridamole had any beneficial effect independent of aspirin. The results of our investigation suggest that the addition of dipyridamole to aspirin does not decrease acute PTCA complications compared to aspirin alone. There were no differences in post-PTCA Q-wave myocardial infarction, emergency coronary artery bypass surgery or death between the aspirin group and the aspirin plus dipyridamole group. By combining the results of our study with the results from Schwartz et al, it may be concluded that aspirin therapy before PTCA is better than no therapy, and that the addition of dipyridamole to aspirin therapy is not beneficial. Neither study was designed to compare aspirin alone or dipyridamole alone with placebo, and whether aspirin is equal to dipyridamole in regard to post-PTCA complications remains unknown. However, because of recent reports of oral dipyridamole-induced myocardial ischemia<sup>20,21</sup> and the additional cost of this drug compared with aspirin, we no longer use it in patients undergoing PTCA. Furthermore, aspirin has been shown to decrease the incidence

of fatal myocardial infarction in asymptomatic men and thus may provide additional protection in patients with known coronary artery disease.<sup>22</sup>

The next question is how much aspirin is enough, given that not all patients can tolerate the gastrointestinal side effects of high dose aspirin. In a prospective randomized trial, we compared low dose aspirin (80 mg a day) versus high dose aspirin (1500 mg a day) as pretreatment of patients undergoing PTCA.<sup>23</sup> We found that the incidence of Q-wave myocardial infarction, emergency surgery, death and restenosis was similar in the low versus high dose aspirin groups. In addition, many patients could not tolerate high dose aspirin after discharge mainly due to gastrointestinal side effects. It is now our policy to pretreat all patients who undergo PTCA with aspirin 325 mg a day and continue it indefinitely.

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#### **Percutaneous Transluminal Coronary Angioplasty in the Setting of Large Intracoronary Thrombi**

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A cohort of 112 consecutive patients with angiographically defined intracoronary thrombi was treated with percutaneous transluminal coronary angioplasty and followed prospectively to determine early and late outcomes. Coronary angioplasty using a treatment modality of intravenous and intracoronary heparin, antiplatelet agents and prolonged inflations with oversized balloons (balloon:vessel ratio, 1.2:1) resulted in clinical success in 103 patients (92%) at hospital discharge. No periprocedural thrombolytic therapy was used and prolonged pretreatment with heparin was not routinely used. Four patients (3.5%) required elective coronary bypass surgery, and 4 patients (3.5%) required emergency coronary artery bypass grafting because of abrupt closure. Late clinical follow-up (mean 7 months) was available in 99 of the 103 successfully treated patients (96%). Seventy-three percent of patients were asymptomatic at followup, and 27% had class I or II angina. No patients had a late myocardial infarction. Elective coronary artery bypass surgery was required in 3 patients (3%) and repeat coronary angioplasty in 17 patients (17%). There were 2 late cardiac deaths at 7 months. Ninety-four patients (95%) had an event free follow-up defined as absence of coronary artery bypass surgery, myocardial infarction or death.

In conclusion, coronary angioplasty alone, using intracoronary heparin and prolonged balloon inflations with relatively oversized balloons may be helpful to achieve a high initial success rate, low incidence of in-hospital complications and excellent long-term results in patients with intracoronary thrombus.

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ecent angiographic, angioscopic and pathologic studies demonstrate that an intracoronary thrombus is frequently observed in the clinical setting of unstable myocardial ischemic syndromes. Intracoronary thrombi have been observed angiographically in patients with unstable angina (range 6 to 37% of patients).1-5 Many of these patients subsequently become candidates for interventional procedures. There is little prospective data available concerning the outcome of patients with intracoronary thrombus who undergo coronary angioplasty. In several retrospective studies of such patients, increased complications have been noted in the periangioplasty period.6-8 Because of these reports, many consider coronary angioplasty relatively contraindicated in this patient population. This has led to speculation that additional technologies such as rotational devices or laser balloon angioplasty may eventually have a role in the treatment of patients with intracoronary thrombus. Douglas et al9 reported that prolonged pretreatment (mean 7 days) with intravenous heparin may be beneficial in the treatment of patients with large intracoronary thrombus before coronary angioplasty. Although effective in decreasing thrombus, this strategy required prolonged hospitalization and the final outcome of angioplasty was not reported. In our clinical practice, we noted favorable results using larger balloons in the treatment of intracoronary thrombus. Therefore, we designed this study to evaluate prospectively the role of coronary angioplasty using intravenous and intracoronary heparin, antiplatelet agents and prolonged inflations with relatively oversized balloons for the treatment of severe coronary stenosis accompanied by a large intracoronary thrombus.

#### **METHODS**

Patients: Between November 1987 and November 1988, 778 consecutive patients undergoing 850 percutaneous transluminal coronary angioplasty (PTCA) procedures at the Minneapolis Heart Institute were analyzed for the presence of intracoronary thrombus. Our sample consisted of 112 consecutive patients who met the criteria for the presence of angiographic thrombus. Among this group were 16 patients with totally occluded vessels. Patients who had coronary angioplasty within 6 hours of an acute myocardial infarction were excluded from analysis. All patients underwent PTCA on an elective basis. The patient demographic and clinical data are listed in Table I.

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ABLE I Clinical Characteristics of	112 Patients
Age (yrs)	59 ± 11
Sex: M/F	87/25
Duration of angina (wks)	4 ± 1
Unstable angina (%)	45 (40)
Recent myocardial infarction	36 (32)
(≤30 days) (%)	
Thrombolytic therapy	32 (22 TPA, 10 SK)
Multivessel disease (%)	55 (49)
Global left ventricular function (%)	
>45%	76 (67)
35 to 44%	28 (26)
25 to 34%	7 (6)
<25%	1(1)

Multivessel coronary angioplasty was attempted in 28 of these 55 patients. Multivessel disease was defined as >50% stenosis in another main epicardial vessel. SK = streptokinase; TPA = tissue plasminogen activator.

Protocol: PTCA was performed via the femoral approach in all patients. Patients were premedicated the evening before and day of the procedure with aspirin 325 mg, dipyridamole 75 mg and nifedipine 10 mg. All patients were then maintained on aspirin 325 mg orally once a day and calcium antagonists for 6 months after PTCA. Immediately before PTCA, all patients received 10,000 U of intravenous heparin and 3,000 U of intracoronary heparin. Additional intravenous or intracoronary heparin was administered for procedures >1 hour in duration. The heparin dosage in many patients was adjusted to maintain an activated clotting time of 300 seconds. Fentanyl, 50 to 150 µg, was administered intravenously before the first balloon inflation as a sedative analgesic. Frequent and prolonged balloon inflations were used with balloons selected to achieve a mean balloon:vessel ratio of 1.2:1. All patients were maintained on intravenous heparin for 8 to 12 hours after PTCA to achieve a partial thromboplastin time of 60 to 120 seconds.

The angioplasty strategy was somewhat modified. An Amplatz left 1 guiding catheter was routinely used for right coronary artery angioplasty, an Amplatz left 2 guiding catheter for left circumflex artery angioplasty and a Judkins left 4 guiding catheter for left anterior descending angioplasty. These guiding catheters were chosen to provide maximal support to allow for the delivery of an oversized balloon as the primary device. The most frequent balloon used was the USCI Low Profile Steerable. Although this balloon has a suboptimal profile, it has the advantage of greater balloon dilating length (25 mm) and versatility in achieved balloon size because of increased balloon compliance. We deliberately chose aggressive balloon sizing in this protocol. In most cases, further upsizing was achieved by increasing the balloon dilating pressure. Intracoronary nitroglycerin was given before dilation.

For the initial inflation, the balloon was centered on the thrombus and not the stenosis. In some cases, the first inflation failed to restore anterograde flow as the balloon was not always centered on the stenosis. In that event, the balloon was then promptly repositioned on the stenosis for a 45-second dilation, and flow was re-

**Definitions:** An intracoronary thrombus was defined as an intraluminal filling defect visualized in multiple

views occuping >50% of the coronary artery lumen. In the case of total occlusion, a thrombus was considered to be present in a totally occluded vessel if at the site of total occlusion, a convex contrast outline was identified and angiographic staining was present. A technical success was defined as a residual stenosis of <50% after PTCA and a residual gradient of <15 mm Hg (if measured). A clinical success was defined as a technical success in the thrombus-laden culprit vessel, an absence of Q-wave myocardial infarction, emergent coronary artery bypass surgery or recurrent angina pectoris at discharge. Routine post-PTCA exercise tests were not done. Patients who required elective predischarge coronary bypass surgery were considered unsuccessful. Patients with technical success and a small non-Q-wave myocardial infarction who were angina free at hospital discharge were considered clinically successful. Intimal dissection, restenosis and unstable angina were defined in accordance with the National Heart, Lung, and Blood Institute PTCA Registry definitions. 10 Both preand post-PTCA mean percent diameter stenoses were determined by measuring the lesion in 2 nearly orthogonal views with computerized calipers. Balloon:vessel ratio was determined by measuring the inflated balloon profile on the cineangiogram with computerized calipers. The length of the intraluminal filling defect was measured with an electronic caliper and recorded as thrombus length. Event free follow-up was defined as absence of myocardial infarction, coronary artery bypass surgery or death.

**Follow-up:** Late clinical follow-up (mean  $7 \pm 3$  months) was available in 99 of 103 successfully treated patients (96%). Variables assessed at the follow-up evaluation included anginal status, need for coronary artery bypass surgery or coronary angiography with subsequent repeat coronary angioplasty.

#### RESULTS

Immediate results: Technical success was achieved in 93% of patients. Figures 1 and 2 show a case example. Mean percent diameter stenosis was reduced from 79 ± 16 to 27 ± 21% after PTCA. Transstenotic gradient was reduced from  $48 \pm 18$  to  $12 \pm 7$  mm Hg. The mean number of dilations was 5, and mean pressure was 9 bar. The mean duration of balloon inflation was 115 ± 47 seconds per inflation, and mean balloon: vessel ratio was 1.2:1 (range 1.09 to 1.32). The left anterior descending coronary artery was dilated in 47, the right coronary artery in 44 and the left circumflex in 26 patients. Multivessel coronary artery disease was present in 55 patients (49%), and multivessel PTCA was performed in 28 patients. Clinical success, as defined previously, was achieved in 103 patients (92%) with intracoronary thrombus treated with PTCA.

Complications: Angioplasty was unsuccessful in 9 patients (8%). Emergency coronary artery bypass surgery was required in 4 patients (3.5%), and 1 of them had a Q-wave myocardial infarction. Elective coronary artery bypass surgery for unsuccessful PTCA was required in 4 patients (3.5%). Medical therapy was required in 1 patient considered unsuccessfully treated with PTCA. There were no in-hospital deaths and no

patients demonstrated late vessel closure or late myocardial infarction. Nonobstructive residual thrombus remained in 27 patients (24%) after PTCA. Acute closure after PTCA occurred in 8 patients (7%). All occurred in the cardiovascular laboratory and were successfully treated with further coronary angioplasty at the time of acute closure. Coronary dissection rates were no higher in the patients with intracoronary thrombus. Transient

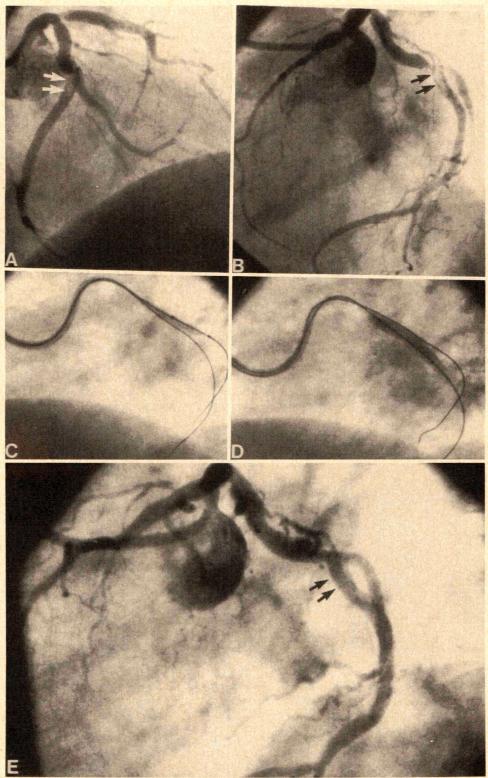


FIGURE 1. Sixty-two-year old man with non-Q-wave myocardial infarction and unstable angina 1 month after myocardial infarction. A, right anterior oblique view demonstrating complex bifurcation stenosis in left circumflex artery with large intracoronary thrombus (white arrows). B, left anterior oblique view again highlighting the intracoronary thrombus (black arrows). C, 3.0-mm balloon in obtuse marginal. D, 4.0 mm balloon in left circumflex artery. E, post-PTCA left anterior oblique view showing absence of intracoronary thrombus and marked improvement in the bifurcation stenosis.

	No.	%
Technical success	104	93
Clinical success	103	92
Emergency CABG—MI	4	3.5
Elective CABG	4	3.5
Repeat angiography	31	31
Repeat angioplasty	17	17
Late death	2	2
Event-free follow-up	94	95

chest pain after PTCA occurred in 18 patients (16%); however, all of these patients were angina free at hospital discharge. Of these patients, only 1 (1%) had an elevated creatinine phosphokinase. Chest pain was more frequently noted after PTCA for this group compared to the general cohort (16 vs 6%, p <0.001). A second PTCA was required in 4 patients (3.5%) during the hospital stay. One patient underwent repeat PTCA within 24 hours and 3 patients underwent repeat PTCA >24 hours after the initial PTCA. All 4 of these patients had residual intracoronary thrombus after the initial PTCA. The 4 patients who required a second PTCA were considered successful. There was 1 (1%) intracoronary embolic event noted as a result of coronary angioplasty in the setting of large intracoronary thrombi.

Follow-up: Of the 103 patients with initial success, 99 (96%) were available for follow-up (mean 7 months). Sixty-nine patients (73%) were clinically asymptomatic. Those with class I or II angina were managed with standard antianginal therapy. Repeat cardiac catheterization was performed in 31 patients with subsequent elective coronary artery bypass surgery performed in 3 patients and repeat PTCA in 17 patients. There were no patients with late myocardial infarction. Late cardiac death (7 months) occurred in 2 patients. Ninety-four patients (95%) had an event-free survival, as previously defined, and a striking 73% were clinically asymptomatic. These data are particularly noteworthy when one considers that of the initial cohort, 32% of the patients had experienced a recent nontransmural myocardial infarction with postinfarction chest discomfort, and 40% had unstable angina (Table II).

#### DISCUSSION

Technical factors: Considerable controversy surrounds the impact of balloon sizing on acute complications of PTCA. One report found that large PTCA balloons resulted in less restenosis (5 vs 36%, p <0.01), and no increase in coronary dissection. 11 Other studies have yielded similar results. 12,13 More recently in a prospective trial, Roubin et al14 noted that the use of larger PTCA balloons was associated with higher acute complications. In our experience, significant intracoronary thrombus required large balloons for optimal initial results and formed the basis for the intention to treat patients with intracoronary thrombus with large PTCA balloons for this study. In the report by Roubin et al,14 large balloons were associated with more myocardial infarction (7.7 vs 3%, p = 0.056) and more emergency surgery (7.7 vs 3.6%, p = 0.015). In our study, we did not observe this higher rate of acute complications associated with larger PTCA balloons in the treatment of patients with intracoronary thrombus.

Published reports suggest that the presence of angiographic thrombus represents a marker for a high risk, if not a relative contraindication, to balloon angioplasty. The initial report by Mabin et al<sup>6</sup> retrospectively identified 15 patients with intracoronary thrombus who underwent coronary angioplasty of a thrombus-laden ves-

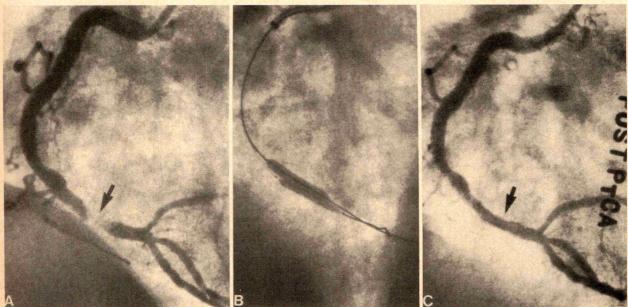


FIGURE 2. Fifty-five-year old man 4 days after myocardial infarction with unstable angina. A, left anterior oblique view demonstrating distal right coronary artery stenosis with intracoronary thrombus. B, simultaneous inflation of 3.5-mm balloon and 2.5mm probe. C, post-PTCA angiography showing marked improvement in the stenosis and absence of intracoronary thrombus.

sel. In this early series, 73% had complete and permanent closure of the dilated artery. Sugrue et al<sup>7</sup> reported on 34 patients with intracoronary thrombus who underwent coronary angioplasty. In this later series, the rate of acute closure had decreased to 24% with 9% of patients refractory to repeat PTCA. Both of these studies involved small numbers of patients and retrospective inhospital events such as myocardial infarction, rate of emergency surgery or death were not reported. Longterm follow-up data were also not available. In a more recent study, Deligonul et al8 retrospectively identified 45 patients with intracoronary thrombus undergoing PTCA. They reported an emergency surgery rate of 9% and distal embolization in 11 patients (24%). In the present study, the rate of acute closure was 7%, the urgent surgery rate 3.5%, distal embolization rate 1% and the overall clinical success rate was 92%. This present study does not define the relative contribution of increased operator experience, intracoronary heparin, prolonged dilations with oversized balloon or modified dilating strategy in improving the results of PTCA in the presence of intracoronary thrombus.

The rate of distal embolization as reported by Deligonul was 24% versus 1% observed in our series. We hypothesized that dilatation with a small balloon initially may result in macrofragmentation of the thrombus and did not allow for adequate extrusion and compression. This 1% incidence of embolization in our series was quite low, but nonetheless remains higher than the 0.1% rate of embolization for the general cohort of patients undergoing PTCA reported by the National Heart, Lung, and Blood Institute Registry. 15

Mechanism: The mechanism of coronary angioplasty of severe coronary stenoses has been extensively studied. 16-19 Little is known about the potential mechanisms involved in the diminution of thrombus via angioplasty. We suggest 3 possible mechanisms: fragmentation, compression and extrusion. Sanborn et al<sup>19</sup> have demonstrated that fragmentation and microembolization occur even with routine angioplasty in the absence of intracoronary thrombus. In the presence of thrombus, the fragmentation and distal embolization would be expected to increase. Despite this anticipated greater extent of embolization, there were few angiographic findings for micro- or macroembolization despite careful review of all post-PTCA cineangiograms. Distal emboli were noted in 1 patient who did not have creatinine phosphokinase elevation. The "no reflow phenomenon" was not observed in our series and similarly no instance of diffuse microvascular staining was noted. These events are thought to represent microemboli and have been described as complications of saphenous vein graft angioplasty.<sup>20</sup> Additionally, except for 1 patient sent for urgent surgery, there were no Q-wave myocardial infarctions noted and only 1 patient (1%) had minor creatinine phosphokinase elevation.

The final proposed mechanism is extrusion. This was evident angiographically in this series. When residual thrombus was identified, it was frequently identified as a thin layer adherent to the vessel somewhat proximal and distal to the original thrombus. If extrusion is in

fact important, then a somewhat longer balloon would present a greater surface length to allow for more effective extrusion.

These results suggest that coronary angioplasty in the setting of intracoronary thrombus may be more safely performed than previously reported.

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### **Medical Costs of Coronary Artery Disease** in the United States

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A model has been developed to determine the cost of coronary artery disease (CAD) based on the 5 primary events identified in the Framingham Study: acute myocardial infarction, angina pectoris, unstable angina pectoris, sudden death and nonsudden death. The costs for diagnostic and therapeutic service for patients with CAD were linked to medical decision algorithms outlining the diagnosis and management of patients with

Because CAD is a changing illness not represented by a single event, the algorithm tracked patients for 5 years after the time of diagnosis, or until death, to develop average cost estimates. The estimated 5-year costs (in 1986 United States dollars) of the 5 CAD events were: acute myocardial infarction \$51,211, angina pectoris \$24,980, unstable angina pectoris \$40,581, sudden death \$9,078 and nonsudden death \$19,697. The costs of major CAD surgical procedures were also calculated because of their impact on health care costs for patients with CAD. These include: coronary artery bypass surgery per case over 5 years \$32,465, and angioplasty per case over 5 years \$26,916. The high cost of CAD reflects the improved technology and more effective and expensive therapies now available.

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7ith United States health care costs currently exceeding \$500 billion annually, there is increased interest in the determinants of expenditures. There has been little research into the total or lifetime cost of medical care for patients with coronary artery disease (CAD), although it represents a leading cause of health care expenditures. We have compiled cost figures and developed medical decision algorithms based on the diagnostic and therapeutic options and probable outcomes for the 5 primary CAD events examined in the Framingham Study. These include acute myocardial infarction (AMI), angina pectoris, unstable angina pectoris, sudden death and nonsudden death.1 We then used these algorithms to estimate the cost of CAD medical care for 5 years after diagnosis, or until death, whichever was earlier. In general, the cost was calculated by multiplying the expected frequency of the test or treatment by its price. The estimated costs often were substantially different from those previously reported,<sup>2,3</sup> in part because the use of medical algorithms and assessment of costs over 5 years allowed a more complete analysis of CAD expenses. This article is not intended to be a review of the efficacy or indications for specific procedures or tests, but rather an analysis of current CAD costs based on data from medical facilities with significant experience in CAD diagnosis and treatment.

#### **METHODS**

In developing a medical cost model, we reviewed the literature on initial CAD events as defined in the Framingham Study, and on the cost and outcome of coronary bypass surgery, thrombolytic therapy and angioplasty. Because of differences in study design, geographic regions and populations, it was difficult to consolidate published study results. Therefore, a group of knowledgeable cardiologists who represented different geographic regions of the US were selected as a consultant panel. The cardiologists generally validated the therapeutic options, projected outcomes and prices that were used. From the collected data, medical decision algorithms were developed to show expected therapies and outcomes for each CAD event. Our decision algorithms are detailed in an Appendix, available upon request.

To estimate costs for each decision made in the CAD treatment algorithms, prices for approximately 70 different procedures, hospital services, medications, laboratory tests, diagnostic services and other medical services were obtained from 3 main sources that will be discussed. All prices used in our model are presented in 1986 US dollars. (A detailed list of specific tests, proce-

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**TABLE I** Abbreviated List of Prices Used in Coronary Heart Disease Model: Annual Cost in 1986 US Dollars

Item .	Price (\$)	Source
AMI hospitalization	4,134	Houston
Ambulance	70	Houston
Blood sugar test	7	HCFA
CCU daily average charges	1,120	Houston
Chest x-ray (2 views)	62	Houston
Complete blood count	8	HCFA
Echocardiogram	139	Houston
Electrocardiogram and interpretation	49	HCFA
Electrolytes	8	HCFA
Holter monitor	285	Houston
ICU daily average charges	970	Houston
MD outpatient visit	47	HCFA
Nineteen chemistry tests	22	HCFA
Nuclear ventricular study	700	Houston
PTCA physician fee	1,412	Houston
Regular care bed per diem	511	Houston
Three chemistry tests	3	HCFA
Treadmill	198	Houston
Urinalysis	6	HCFA

AMI = acute myocardial infarction; CCU = coronary care unit; HCFA = Health Care Financing Administration; ICU = intensive care unit; PTCA = percutaneous translumial coronary appioplasty.

dures and medications used in each coronary event algorithm is available as part of the Appendix.)

In 1985, the Health Care Financing Administration (HCFA) maintained a list of national average prices for 110 high-frequency physician services paid by Medicare. HCFA did not update this list in 1986. For all CAD medical services identified in our decision algorithms and found on this list, HCFA national average prices were used.

Most drug prices were obtained from 1986 pharmaceutical price surveys from IMS America, a data resource group (Plymouth Meeting, Pennsylvania). For each category of medication (e.g., diuretics,  $\beta$  blockers, angiotensin-converting enzyme inhibitors) average daily consumption and retail prices for the largest selling medication in that category were used to compute the average medication costs per patient.

All other medical prices were obtained from Houston area surveys. Both HCFA and Houston hospital prices were generally considered similar to, or lower than, those prevailing in the panelists' locales. For this reason, and because of the relatively high rate of medical inflation, the prices we have used are conservative. Table I provides a list of some of the key prices used in the analysis. A detailed pricing list is available in the Appendix.

#### RESULTS

Acute myocardial infarction: In the US, approximately 1.5 million people have an acute myocardial infarction (AMI) yearly.<sup>4</sup> In 1983, 676,000 primary discharge diagnoses from nonfederal, short-term hospitals were for AMI.<sup>5</sup> Not all cases resulted in hospitalization,<sup>4,6</sup> mostly because of sudden death and unrecognized AMI. While the Framingham Study calculated the risks of AMI for both recognized (hospitalized) and

**TABLE II** Expected Cost of Myocardial Infarction Complications (in \$)

Extension of infarction	2,151
Congestive heart failure	900
Pulmonary edema	392
Cardiac arrest	242
Cardiogenic shock therapy	
Medical therapy	68
Medical therapy and aortic balloon	323
Aortic balloon and bypass surgery	135
Angioplasty	161
Permanent pacemaker	40
Temporary pacemaker	36

**TABLE III** Five-Year Outcome of Patients Receiving Medical Therapy After Myocardial Infarction

Condition	Prevalence (%)	Added Expected Cost for Acute Myocardial Infarction (\$)		
No treatment	15	0.00		
Angina pectoris	35	4,863		
Congestive heart failure	14	1,406		
Reinfarction	25	7,123		
Death	30	2.033		

**TABLE IV** Framingham Coronary Artery Disease Events: Five-Year Expected Total Cost per Case

	Average Cost (\$)
Acute myocardial infarction	51,211
Angina pectoris	24,980
Unstable angina pectoris	40,581
Sudden death	9.078
Nonsudden death	19.697

**TABLE V** Coronary Artery Disease Procedures: Five-Year Expected Total Cost per Case (\$)

Angioplasty	26,916	
Coronary bypass surgery	32,465	

unrecognized (not hospitalized) AMI, we have considered only patients who were hospitalized with a recognized AMI.

The costs for those who died from an AMI and were either not brought to the hospital or died in the emergency room are considered in the section on sudden death. The costs for patients who died in the hospital after admission for an AMI are reviewed in the section on nonsudden death. The AMI patients considered in this section have been defined as those who were admitted and survived hospitalization. Figures 1, 2 and 3 diagram our decision algorithm. Tables II, III, IV and V list some of the specific costs of these algorithms.

In 1980, the average total length of hospitalization for an AMI was 12.9 days. Patients who were subsequently discharged were in the hospital an average of 14 days, while those who died after admission were in the hospital an average 8.5 days. By 1983, the length of hospitalization for AMI had decreased to approximately 11 days. We used 10 days as the average length of

stay. Change in the length of hospitalization alters the cost of AMI. A decrease of 1 day in regular care lowered the expected average cost of AMI by \$511.

Emergency room care and hospitalization in the coronary care unit for 3 days, intermediate care for 4 days and regular care for 3 days, plus inpatient cardiac rehabilitation, laboratory fees and medications added \$13,670 to the expected cost of AMI.

COMPLICATIONS OF INFARCTION: Approximately 60% of patients hospitalized with an AMI experienced complications. Cardiac arrhythmias, varying degrees of left ventricular failure and continued chest pain often resulted in a more prolonged hospital course.8-10 While complications from AMI continue to be a cause of concern and extensive study by clinicians, they contributed little to the total expected cost of AMI, because of the relatively small number of patients who suffered significant costly complications (Table II). The greatest single

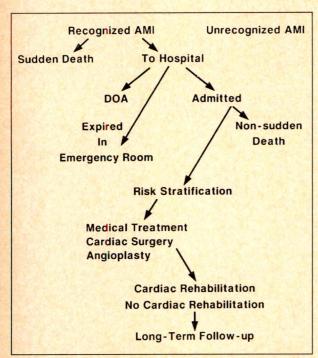


FIGURE 1. Decision algorithm for acute myocardial infarction.

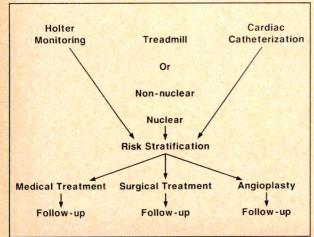


FIGURE 2. Decision algorithm for Holter monitoring, treadmill or cardiac catheterization treatment of postinfarction patients.

added expected cost was \$2,151 for extension of an AMI, which is estimated to occur in 7% of patients.

RISK STRATIFICATION FOR INFARCTION: Holter monitoring, treadmill testing and cardiac catheterization have been used in recent years to assess the risk of future cardiac events occurring in postinfarction patients (Figure 2). Holter monitoring has been used to detect arrhythmias and both symptomatic and silent myocardial ischemia. The consultant panel estimates varied widely in the estimate of the use of Holter monitors in AMI patients; the range was 20 to 100%. We used a 50% rate in our base case analysis.

An exercise treadmill test was performed on 75% of patients either before discharge or within 6 weeks of hospitalization. 11-13 We estimated that 60% of tests were nuclear exercise and 40% were non-nuclear exercise testing. For the AMI patient, Holter monitoring and exercise testing added \$1,718 to the average cost of AMI. The price of an outpatient cardiac rehabilitation was \$2,430 per patient. Because only 15% of patients who had an AMI participated, outpatient cardiac rehabilitation added a small amount to the average cost of AMI.

At the initial hospitalization or within 3 months, 30% of patients who survived a recognized infarction and had not received thrombolytic therapy had heart catheterization, which added \$847 to the average AMI cost. Among these patients, 25% had coronary bypass surgery (adding \$2,191 to the average cost), 33% had angioplasty (adding \$2,398 to the average cost) and 42% received medical therapy (adding \$860 to the average cost).

THROMBOLYTIC THERAPY: Coronary thrombosis has been reported in 70 to 90% of patients with AMI.14 Successful thrombolytic therapy can limit infarct size, preserve left ventricular function and reduce hospital mortality. 15-17 The success of thrombolytic therapy with streptokinase was related to the elapsed time between the onset of AMI and the initiation of therapy. If >6 hours elapsed between the AMI and thrombolytic ther-

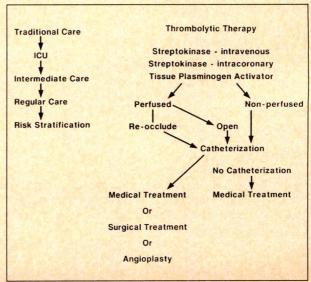


FIGURE 3. Decision algorithms for traditional care versus thrombolytic therapy.

apy, then the effect of thrombolysis on mortality was significantly blunted.<sup>18</sup> Because the onset of the AMI was >4 hours among most patients who presented to the hospital emergency room,<sup>19</sup> we estimated that only 25% of patients were candidates for thrombolytic therapy, and 75% received traditional care for their AMI.

Streptokinase thrombolytic therapy can be given by either the intracoronary or intravenous route to patients with an AMI (Figure 3). Because intracoronary thrombolytic therapy required a readily available cardiac catheterization facility and trained personnel, 20 10% of patients received intracoronary thrombolytic therapy and 90% received intravenous streptokinase.

Seventy-five percent of patients who received intraccoronary streptokinase and 50% who received intravenous streptokinase were successfully reperfused.<sup>21</sup> A 20% reocclusion rate for intravenous streptokinase and a 17% reocclusion rate for intracoronary streptokinase were used in the algorithm.

Tissue plasminogen activator, a naturally occurring human protein capable of inducing clot lysis, <sup>22,23</sup> was recently approved by the Food and Drug Administration. Intravenous tissue plasminogen activator with a reperfusion rate of 75% has appeared as effective as intracoronary streptokinase. <sup>23</sup> Among patients successfully reperfused, 50% had angioplasty, 25% bypass surgery and 25% medical therapy. For patients not successfully reperfused, 42% received medical therapy, 25% bypass surgery and 33% angioplasty.

Among patients younger than 75 years of age who received thrombolytic therapy followed by heparin, 11% had significant bleeding problems.<sup>24</sup> Bleeding complications were reported in 7% of patients who received intravenous heparin in an amount sufficient to keep the partial thromboplastin time 2 times the control value.<sup>25</sup> Bleeding complications from the use of streptokinase and heparin added only \$31.50 to the average AMI

The 5-year cost of thrombolytic therapy included the costs of the increased number of heart catheterizations, angioplasties and bypass surgeries for these patients compared to patients who received traditional care for AMI. If all patients who received thrombolytic therapy were given only streptokinase, an average of \$4,197 was added to the expected cost of an AMI. The price of streptokinase was \$220 per patient. If only tissue plasminogen activator therapy was used as the thrombolytic therapy, \$4,733 was added to the expected cost of AMI. The price of the medication was \$2,200 per patient treated.

OUTCOME AFTER INFARCTION: The Framingham Study's 5-year follow-up of men and women who had an initial AMI and were taking medical therapy<sup>26</sup> (Table III) was used to predict the incidence of medical events. We estimated that 92% of treated patients would be alive at 1 year and that the 5-year results among patients who received coronary bypass or angioplasty would be identical to those who had not had a previous AMI. The cost of medical therapy per patient for 5 years added \$3,865 to the expected AMI cost. In our study, the expected total cost over 5 years for a patient hospitalized with AMI was \$51,211.

Nonsudden death: Approximately 10% of the patients admitted with a diagnosis of AMI died in the hospital. By the Framingham Study definition, they comprised the nonsudden death group. The expected cost for nonsudden death was \$139 for the emergency room plus \$13,254 for the hospitalization. The average length of hospitalization for those who died was 8.3 days. Compared to other AMI patients, the cost of the shorter hospitalization was offset by the cost of resuscitation.

Sudden death and sudden death resuscitated: In the US, 650,000 people die yearly from CAD, with sudden death accounting for 50% of deaths. 4,27 We used the Framingham Study definition of a 1-hour time period between the change from a stable clinical status to death.1 Among those resuscitated from sudden death, 90% had underlying CAD.<sup>28,29</sup> Figure 4 gives an overview of the algorithm for sudden death. It has been predicted that 25 to 30% of those who suffered sudden death could be resuscitated and eventually discharged alive from the hospital.30,31 Our algorithm was more conservative. Of 100 patients with sudden death, 68 died outside the hospital and were taken to a funeral home. Of the 32 patients transported to the hospital by ambulance, 26 patients were successfully stabilized and hospitalized. Among the 26 patients hospitalized after successful resuscitation, 5 were assumed to have died in the hospital, while 21 were discharged alive. The cost of the ambulance, emergency room and hospitalization, including 3 days in the coronary care unit, 5 days in intermediate care and 4 days in regular care, added \$2,840 to the expected cost of sudden death.

Approximately 10 to 15% of patients resuscitated after sudden death and ultimately discharged from the hospital are left with significant morbidity.<sup>31</sup> The cost of care for those who did not fully recover was not included in this study. For patients who survived cardiac arrest, cardiac catheterization and electrophysiologic test-

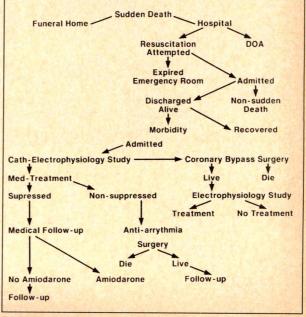


FIGURE 4. Algorithm for sudden death.

ing have been recommended.32 The 15% with significant morbidity had two 24-hour Holter monitors, and subsequently were given antiarrhythmic therapy. The remaining 85% of patients had heart catheterization, adding \$575 to the expected cost of sudden death, and an electrophysiologic study, adding \$344 to the expected cost of sudden death.

Forty percent of the resuscitated patients who were catheterized had coronary bypass surgery, with a survival rate of 92%, which added \$2,532 to the total cost. Patients who survived the initial surgery had a second electrophysiologic study, which added an additional \$138 to the cost of sudden death. Approximately twothirds of these patients also required antiarrhythmic therapy, which added over 5 years \$190 per case to the average cost of sudden death. Seventy-two percent of these patients lived for at least 5 years after bypass.33

Sixty percent of the patients who had catheterization and an electrophysiologic study after resuscitation from sudden death were treated medically. The 5-year expected cost per patient treated medically was \$2,059. This cost included a follow-up electrophysiologic study to judge the effectiveness of the antiarrhythmic medication, plus additional testing and therapy. Among patients treated with antiarrhythmic therapy, only 26% experienced adequate suppression of their arrhythmias based on a follow-up electrophysiologic study.<sup>32</sup> Approximately 10% of patients not adequately suppressed underwent antiarrhythmic surgery, which had an expected cost of \$28,600 per case. Overall, because only about 1% of the total number of patients who were resuscitated after sudden death had this surgery, it added only \$1,747 to the average expected cost of sudden death.

Patients who were neither candidates for antiarrhythmic surgery nor adequately suppressed on antiarrhythmic therapy were given amiodarone, with a 50% successful suppression rate.34 However, after 2 years, amiodarone was discontinued in 20% of these patients because of drug toxicity. If all patients not treated surgically or suppressed on other antiarrhythmics were giv-

en amiodarone, it would add \$449 to the average cost of sudden death over 5 years.

Among patients resuscitated from out-of-hospital cardiac arrest who survived the initial hospitalization, the 4-year mortality ranged from 25 to 50%.31 Overall, the average total cost per case of sudden death/sudden death resuscitated was \$9,078 over a 5-year period.

Angina pectoris: Approximately 5 million people in the US have angina pectoris or a history of a previous AMI.4 In 1983, angina pectoris was the primary diagnosis listed for 278,000 hospital discharges, and accounted for 1.488,000 hospital days. One difficulty in evaluating the prevalence of angina in the population is that it may fluctuate in intensity in the individual patient. A patient who at 1 examination had typical angina pectoris could be free of symptoms at a subsequent examination.35 During the first 8 biennial examinations in the Framingham Study, 32% of men and 44% of women had transient or nonpersistent angina.

Over a 5-year period, one-half of patients with angina were assumed hospitalized for an average of 6 days because of cardiovascular disease.36 The cumulative survival of patients with CAD receiving medical management was reported to be affected by the presence of left main coronary disease, left ventricular function and patient age. For patients with 1- and 3-vessel CAD, the 4year survival rate was 92 and 68%, respectively.

Over a 5-year period, 40% of patients with angina pectoris had heart catheterization. Catheterization added \$1,255 to the expected cost of angina pectoris. The 1975 to 1979 Coronary Artery Surgery Study reported that about 5% of patients with angina pectoris had surgical intervention annually.<sup>37</sup> This number should decrease as more patients have angioplasty. Among the patients catheterized, 25% had angioplasty, for an additional expenditure of \$2,688, 50% had coronary bypass surgery, adding \$6,493, and 25% continued to receive medical therapy.

Among the 60% of patients in our study who did not have heart catheterization, 40% were not receiving consistent treatment for angina and no cost was ascribed.

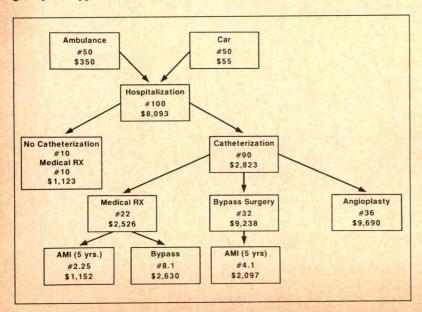


FIGURE 5. Costs of 5-year specific acute myocardial infarction treatments.

The remaining 60% were taking regular daily therapy for angina, adding \$4,317 to the expected angina pectoris cost. In addition, approximately 20% of medically treated patients had an AMI during the 5 years, prompting an additional \$4,091 expenditure. The total cost for each case of angina pectoris over 5 years was \$24,980.

Unstable angina pectoris: In 1983, 130,000 hospital discharges listed unstable angina as the primary diagnosis. In reality, this figure was probably larger. It is often difficult to separate unstable angina from an AMI. It is also likely that many of the hospitalizations for angina pectoris were actually for unstable angina.

Patients admitted with unstable angina pectoris were in the coronary care unit for 2 days, intermediate care unit for 3 days and regular care unit for 2 days. The cost of hospitalization, including medication and non-invasive testing, added \$8,093 to the expected unstable angina cost.

Because of the potential for infarction or sudden death, about 90% of unstable angina patients had heart catheterization during the initial hospitalization. Heart catheterization added \$2,823 to the expected cost of unstable angina. The remaining patients who did not have cardiac catheterization were given medical therapy, adding \$1,169 to the cost over 5 years. The number not catheterized may increase in the future with the use of early exercise testing.<sup>38</sup>

Approximately 35% of patients diagnosed with unstable angina pectoris had coronary bypass surgery within a few weeks, with a surgical mortality rate of 4%. This surgery added an additional \$9,238 to the expected cost of unstable angina. At the end of 1 year, 95% of the patients were alive, and 13% had had an AMI. An AMI after bypass surgery added \$2,097 to the expected cost. The 4-year surgical survival rate was 88%. Forty percent with unstable angina pectoris who had heart catheterization had angioplasty. The consultant panel generally felt that angioplasty would be used with increased frequency in patients with unstable angina.<sup>39</sup> Angioplasty increased the average cost of unstable angina by \$9,690. Twenty-five percent of those catheterized received medical therapy, for an added cost of \$2,526. For this group, the survival rate was 93% after 1 year and at 5 years was 87%. 40 Ten percent of patients had an AMI during year 1. An additional \$1,152 was added by AMI that occurred during the 5-year follow-up.

Over a period of 30 months, approximately 36% of those who were initially treated medically required bypass surgery, 40 adding \$3,799 to the expected cost of unstable angina. From the available data, we have used only the first year AMI incidence rate after coronary bypass. Altogether, the average cost for unstable angina per case over 5 years was \$40,581.

ANGIOPLASTY FOR ANGINA PECTORIS: Percutaneous transluminal coronary angioplasty was initially introduced in 1977 by Gruentzig for the treatment of a proximal stenosis in 1 of the 3 main coronary vessels. Subsequently, the indications for angioplasty have been extended 41

Angioplasty for CAD was initially successful 85% of the time, with 90% of the patients having no or de-

creased angina, and 10% unchanged. When angioplasty was used to treat angina pectoris, the average length of hospitalization was 2 days. The patients had heart catheterization at the time of angioplasty and were monitored for 4 hours. Successful angioplasty, including preangioplasty exercise testing, hospitalization and medication, had an expected cost of \$6,706. The 5-year medical follow-up among those with successful angioplasty, including annual exercise testing and medication, added \$5,381 to the expected cost of angioplasty.

As experience with angioplasty has increased, the complication rate has decreased.<sup>42</sup> We report figures from medical facilities with experience in angioplasty. Angioplasty failed in 15% of the cases. The failures reflected a 1% overall mortality rate,<sup>41</sup> an AMI rate of 2.5%<sup>43,44</sup> and a ≥4% emergency coronary bypass surgery rate, usually for coronary artery occlusion or coronary artery dissection.<sup>41</sup> These complications added \$2,579 to the average cost of angioplasty. Surgical standby for angioplasty has been considered essential.<sup>45</sup> Patients in whom angioplasty was not successful had coronary bypass surgery or continued medical treatment,<sup>46</sup> adding \$1,966 to the expected angioplasty cost.

Among patients who had successful angioplasty, 40% had recatheterization, usually within 6 months because of either recurrent angina or a suspicion of restenosis. Among patients who had angioplasty for angina, the reported rate of restenosis at 6 months has ranged between 17 and 47%.47 We have used a restenosis rate of 30%.48 The rate of restenosis without symptoms of angina was reported to be 30%.46 Among patients with detected restenosis, we estimated that 65% had repeat angioplasty, 20% coronary bypass surgery and 15% medical therapy. With repeat angioplasty, there was an 85% success rate. 49 The cost of the evaluation, including treadmill testing, catheterization and subsequent treatment with either medical therapy, repeat angioplasty or coronary bypass surgery, added \$7,664 to the expected cost of angioplasty.

We assumed a 15% restenosis rate over the next 5 years. 48 Among those with late stenosis, 30% had bypass surgery, 60% angioplasty and 10% medical treatment. This did not include patients who had progression of disease in vessels not originally treated by angioplasty.

Over a 5-year period, the average cost of angioplasty for angina pectoris was \$26,916 per case.

CORONARY ARTERY BYPASS SURGERY: Coronary artery bypass surgery is an effective therapy to improve myocardial blood flow in selected patients with CAD,<sup>50</sup> and the number of coronary heart bypass grafts has increased markedly. In 1971, 24,000 such surgeries were performed. In 1985, over 230,000 coronary artery bypass surgeries were performed.<sup>51</sup>

The reported length of hospitalization for coronary bypass surgery has varied. Readmissions, especially in the first year for postoperative surgical problems, raised the average number of hospital days per surgical case. The consultant panel believed that the length of hospitalization after surgery had decreased; we used 10 hospital days for each surgical case. Preoperative care and preoperative catheterization were not included in the cost.

Coronary artery bypass surgical mortality has been related to factors such as patient age and status of the left ventricle.<sup>52</sup> This algorithm used the Coronary Artery Surgery Study registry with a surgical mortality rate of 2.4%.<sup>53</sup>

By 6 months after surgery, approximately 16% of grafts were occluded; thereafter, the annual occlusion rate was about 1%.<sup>52</sup> By 5 years, about 3% of patients had repeat coronary artery bypass surgery. By 10 years 11.4%, and by 12 years, 17.3% of the patients had re-

peat coronary bypass surgery.54

Compared to their preoperative symptoms, by 1 year after surgery, about 87% of patients had no angina pectoris, 10% had less angina and 3% were symptomatically unchanged. By 5 years, while about 90% of patients who had bypass surgery survived, 50% had angina pectoris. 55 Patients who had recurrent angina pectoris after coronary bypass surgery added \$3,588 to the average cost of bypass surgery. If angina pectoris did not recur in the 5 years after surgery, follow-up testing and medication added \$2,218 to the cost of bypass surgery. Over 5 years, the cost of repeat bypass surgery or angioplasty on occluded grafts added \$1,091 to the expected cost of coronary bypass surgery.

The percentage of patients with stenosed bypass grafts for whom angioplasty is appropriate is uncertain. Excellent success has been reported for those who have angioplasty for occluded grafts. <sup>56</sup> The use of angioplasty rather than repeat bypass surgery will affect the cost of bypass surgery. Overall, the average cost per case for

bypass surgery over 5 years was \$32,465.

#### DISCUSSION

There is no systematic data collection source in this country that allows comprehensive, nationally representative, CAD medical cost information to be obtained. We developed a cost model based on published findings and the consultant panel's consensus regarding appropriate treatment and expected outcome for patients with CAD. We believe this model is generally more applicable to all sections of the country than data collected from a specific patient sample. While not attempting to define "ideal" treatment and outcome, the model does reflect current appropriate therapy and documented outcomes.

While we recognize that there is a distinction between prices (charges) and real economic resources, 57 we did not attempt to adjust prices to actual economic cost levels. Our cost analysis more appropriately reflects what a patient or insurer would pay for medical services, rather than the economic costs to hospitals, physicians and other providers to produce these services.

This review has focused on CAD medical costs for each of the 5 Framingham events, plus coronary artery bypass surgery, thrombolytic therapy and angioplasty, for both the initial presentation and the 5 following years. Therefore, these costs are not estimates of the total expected lifetime costs of CAD. CAD is neither a stable single event nor a static phenomenon. Effective long-term treatment requires ongoing diagnostic testing

and therapeutic intervention. Because of this, it is important to assess the cost of CAD therapy over a significant period of time subsequent to the initial diagnosis. The costs included subsequent CAD events expected to occur within this time interval, adjusted for diagnosis-specific 5-year average survival probabilities. Because of continuing rapid changes in medical treatment, we did not project medical costs beyond 5 years of treatment.

The reported cost was determined by multiplying the price of the expected therapy or test by the probability of occurrence for each therapy or test over the ensuing 5 years. An expensive but infrequent complication or treatment could add less to the average cost of an AMI than less expensive but more frequently performed tests or treatments. Surgery for intractable cardiac arrhythmias among sudden death survivors had a price of \$28,600; however, because of the relatively small percent who required the surgery, it added only \$175 to the expected average cost of sudden death. Alternatively, unstable angina costs averaged \$40,581 per patient over 5 years. The high cost reflected the high percent of patients who had expensive diagnostic testing and therapeutic intervention. The frequent use of angioplasty and bypass surgery added \$18,928 to the average cost of unstable angina.

While most medications and diagnostic tests for patients with angina pectoris were relatively inexpensive, over 5 years medical treatment added \$10,634 to the expected cost of angina pectoris (\$4,317 for medication and testing plus \$6,317 for the cost of AMIs among the medically treated group). Medical treatment was provided to a total of 46% of patients with angina. Bypass surgery added \$7,746 (\$1,255 for catheterization plus \$6,493 for surgery) to the average cost, and was used to treat 20% of patients with angina. Although medical therapy and bypass surgery contributed approximately the same to the total cost of angina pectoris, over twice as many patients received medical therapy.

Many tests may have little impact on the cost of CAD. The consultant panel suggested a wide range for the use of Holter monitoring among patients with recent AMI. Although it is an important therapeutic decision, Holter monitoring had only a small impact on the cost of the AMI patient. Whether an AMI patient had Holter monitoring or not, the average net change in cost

for an AMI patient would be \$157.

Sudden death is the least expensive of the 5 Framingham coronary events. It cost \$9,078, which is still a surprisingly large sum of money. While the increased emphasis on resuscitation and rapid transportation of patients to the hospital has saved many lives, it has increased the cost of sudden death and sudden death resuscitated. The percentage of patients who several years ago would have been pronounced dead outside the hospital has decreased; those pronounced dead in the emergency room where resuscitation is attempted has increased. Patients successfully resuscitated have a significant number of sophisticated studies, and may have coronary bypass surgery or surgery for the treatment of arrhythmias.

An example of a therapeutic advance that has also increased the cost of AMI is thrombolytic therapy. Tissue plasminogen activator added \$4,733 to the expected cost of an AMI, while streptokinase added \$4,197. Tissue plasminogen activator was \$2,000 more expensive than streptokinase; however, it added only \$566 to the expected cost of an AMI. Therapy with thrombolytic agents resulted in more survivals and higher health care costs because thrombolytic therapy patients had relatively more heart catheterizations, angioplasties and bypass surgeries.

Another therapy that offered less cost savings than anticipated was angioplasty. While not disputing the medical role of angioplasty, this analysis casts doubt on whether angioplasty will substantially decrease the cost of medical care. In our algorithm, the 5-year cost of angioplasty (\$26,916) was only 17% less than the cost of coronary artery bypass surgery (\$32,465).

Kelly et al<sup>3</sup> reported a 43% lower cost over 1 year of angioplasty compared to coronary surgery among patients with 1-vessel disease. In the Coronary Artery Surgery Study, 27% of patients with angina pectoris who underwent surgery had 1-vessel disease.37 The cost of coronary bypass surgery accounted for \$6,493 of the expected cost of angina pectoris. If we assume that angioplasty was done on every patient with 1-vessel disease, using Kelly's data the amount saved would be 43% of 27% of \$6,493 or \$779. This is a small amount compared to the expected total cost of angina pectoris: \$24,980 per patient. Therefore, even if there were a significant difference in cost between angioplasty and coronary bypass surgery, greater use of angioplasty would have little effect on the overall expected cost of angina pectoris among patients with 1-vessel disease. While the initial cost of successful angioplasty was less than that of bypass surgery, the treatment of restenosis, testing and medication over the following 5 years (\$9,067) significantly added to the total cost of angioplasty. We believe that the 5-year cost reflected a more accurate estimate of the effect of angioplasty on CAD treatment

We have not evaluated the economic impact of quality variations reported in the outcome of CAD therapy, or focused on such issues as the relation of outcome to the volume of bypass surgery performed<sup>58</sup> or physician experience with angioplasty outcome.<sup>42</sup>

Our analysis shows that the major reason for the increased cost of CAD has been the ability to intervene acutely in patients with CAD with new technologies and new therapies, such as thrombolytic therapy and coronary bypass surgery. These new therapies have contributed to the decrease in CAD mortality, improved the quality of life of CAD patients, increased the number of patients who survived a Framingham event and allowed more people to live longer.

We expect newer treatment and technology to continue to increase the cost of CAD. It is apparent that recent innovations in restorative therapy for CAD have substantially increased average medical costs per patient.

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# Left Ventricular Hypertrophy Is Associated with Worse Survival Independent of Ventricular Function and Number of Coronary Arteries Severely Narrowed

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Left ventricular (LV) hypertrophy has been repeatedly shown to be associated with a marked increase in mortality risk. Available data, however, do not provide evidence that the risk associated with the increase in cardiac muscle mass is independent of the severity of preexistent coronary artery disease. In a cohort of predominantly black patients with a high prevalence of hypertension and LV hypertrophy, LV mass as estimated by echocardiography was found to be a powerful prognostic factor independent of ejection fraction and obstructive coronary disease. After excluding patients with either a dilated LV cavity (diastolic internal diameter >5.8 cm) or asymmetric septal hypertrophy (septal:posterior wall ratio >1.5) LV mass/height remained significantly increased in decedents compared to survivors (116  $\pm$  38 vs 131  $\pm$  47 g/m, p = 0.014), while the thickness of the ventricular septum and the posterior wall were even more highly predictive of a fatal outcome (p = 0.003 and 0.001, respectively). After exclusion of patients with eccentric LV hypertrophy, differences in LV muscle mass in survivors and decedents were due entirely to increased thickness of the ventricular wall, and no differences in cavity dimensions or LV ejection fraction were noted. Stepwise regression analysis was used to demonstrate that measures of LV hypertrophy were the most important predictors of survival and eliminated the contribution of all other prognostic factors to the model except the number of stenotic vessels. The relative risk associated with a 100-g increase in mass was 2.1, while a 0.1-cm increase in posterior wall thickness was associated with approximately a 7-fold increase in the risk of dying. These findings suggest that hypertension is an important risk factor for cardiac death over and above its effect on accelerating the development of coronary atherosclerosis and that echocardiographically derived measures of LV hypertrophy can add significant discriminatory information over angiographic data.

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rospective epidemiologic studies have clearly established the increased risk of cardiovascular death associated with left ventricular (LV) hypertrophy. 1-6 Although electrocardiographic measures have been most widely used,4 the echocardiogram is more sensitive and promises to yield crucial new information in this field.7-9 On the basis of present knowledge, however, a challenge can be made to the claim that LV hypertrophy has independent prognostic importance. The principal risk factor for the development of LV hypertrophy is hypertension, 10 and hypertension also accelerates the development of atherosclerosis. LV hypertrophy, therefore, may serve as a time-integrated marker of the exposure to elevated blood pressure and thus more accurately identify persons at high risk for subsequent coronary events. There is further evidence that persons with coronary artery disease have larger LV mass<sup>11,12</sup> as a result of either dilatation of the LV cavity or compensatory segmental hypertrophy, and measures of LV hypertrophy may likewise identify asymptomatic prevalent coronary disease. The association between LV hypertrophy and cardiac mortality may therefore be confounded by hypertension. Studies based on the noninvasive evaluation of cardiac function cannot eliminate the possibility that underlying coronary or cerebrovascular disease contributes to all or part of the increased risk associated with LV hypertrophy. To assess the predictive power of LV hypertrophy independent of coronary artery disease, we undertook a prospective followup study of patients with angiographically defined coronary anatomy and LV function who had echocardiographic measurement of LV mass.

#### **METHODS**

Patient recruitment: The Cook County Heart Disease Registry was established in 1983 to study the clinical epidemiology of coronary artery disease in a predominantly black population. Between June 1982 and December 1988, 1,893 patients underwent cardiac cath-

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TABLE I Cook County Hospital Heart Disease Registry: Descriptive Characteristics of 1,893 Patients Undergoing Cardiac Catheterization

Variable	Coronary Artery Disease (n = 1,115)	Normal Coronaries (n = 778)
Age (yrs)	59 ± 9	56 ± 9*
Men (%)	58	33*
Black (%)	81	73
Hypertension (%)	60	64
Prior AMI (%)	41	13*
No. of coronary arteries narrowed ≥50% in diameter:		
0	10 _ 10 10 PM	778
1	298	
2	301	
3	516	
Ejection fraction (%)	60 ± 16	68 ± 13*
Mean follow-up (weeks)	$123 \pm 96$	$99 \pm 85*$
Survival at 4 years (± SE)	78 ± 2	92 ± 2*
Prevalence of ECG LVH (%)	26	24 <sup>†</sup>

All  $\pm$  data are mean  $\pm$  standard deviation. \* p <0.01; 'p <0.05. AMI = acute myocardial infarction; ECG LVH = left ventricular hypertrophy on electrocardiogram; SE = standard error.

**TABLE II** Descriptive Characteristics of Patients Undergoing Cardiac Catheterization with Normal Size Left Ventricular Chamber Dimensions, by Vital Status

	Survivors	Decedents		
Variable	(n = 700)	(n = 44)	p Value	
Age (yrs)	55 ± 9	57 ± 9	0.01	
Men (%)	41	57	0.01	
Black (%)	78	84	_	
Median family income*	$$17.5 \pm 5.5$	$$16.1 \pm 4.9$	_	
Median years of school	$11.6 \pm 1.4$	$11.4 \pm 0.9$	_	
Blue collar (%)	81	84	0.05	
Medical history				
Hypertension (%)	78	79	-	
Current smoker (%)	36	41	-	
Diabetes mellitus (%)	29	24	-	
No. of coronary arteries				
narrowed ≥50% in diamet	er:			
0	47	16		
1	15	23		
2	13	23		
3	25	39	0.001	
Ejection fraction (%)	$66 \pm 13$	$62 \pm 14$		
Prevalence of ECG LVH (%)	26	49	0.003	

All ± data are mean ± standard deviation.

\* In thousands

Abbreviations as in Table I.

TABLE III Echocardiographic Left Ventricular Hypertrophy as a Predictor of Mortality: Univariate Analysis

Variables	Survivors (n = 700)	Decedents (n = 44)	p Value
LV mass – actual (g)	194 ± 64	222 ± 81	0.007
LV mass/height (g/m)	$116 \pm 38$	$131 \pm 47$	0.014
Ventricular septal thickness (cm)	$1.17 \pm 0.24$	$1.28 \pm 0.30$	0.003
Posterior wall thickness (cm)	$1.14 \pm 0.24$	$1.23 \pm 0.24$	0.001
Systolic internal diameter (cm)	$3.05 \pm 0.66$	$3.04 \pm 0.61$	-
Diastolic internal diameter (cm)	$4.72 \pm 0.55$	$4.74 \pm 0.64$	-
Prevalence of ECG LVH* (%)	51	61	0.019

All ± data are mean ± standard deviation

\* LV mass/height > 100 g/m for women and >120 g/m for men. Abbreviations as in Table I.

eterization as part of a diagnostic evaluation for presumed coronary artery disease. Complete echocardiographic data were available on 920 patients, who were not different from the rest of the cohort in terms of the major descriptors, i.e., age, sex, race and prevalence of other medical conditions, except for a slightly higher prevalence of previous myocardial infarction. The final analytic sample was selected from the patients with echocardiographic data based on the following considerations. Serious confounding of the relation between survival and LV mass may occur by inclusion of patients with LV dilatation because of the inverse correlation between measures of systolic function (i.e., ejection fraction) and LV mass. Thus, patients with a dilated heart will have a low ejection fraction and a large calculated LV mass because of the increased cavity size ("eccentric" LV hypertrophy). In addition the interrelations among LV mass, ejection fraction and survival are different at the higher and lower extremes of ejection fractions; under these circumstances independent effects cannot be identified by standard statistical procedures that control for multiple covariates since an assumption of linearity across the range of values observed is usually required. To avoid this problem a stratified analysis was performed and 155 patients with an LV diastolic diameter >5.8 cm were excluded. Twenty-one patients with severe asymmetric septal thickening, defined as a ratio of the ventricular septum to posterior wall >1.5, were also excluded, yielding a final sample of 744 persons. While many patients with asymmetric septal hypertrophy were likely to have a form of hypertrophic cardiomyopathy secondary to hypertension, 10 and none had outflow obstruction, we felt these exclusions were necessary to provide a homogenous analytic sample with a normal sized left ventricle (i.e., "concentric" LV hypertrophy). All analyses were repeated with the inclusion of patients with a dilated LV chamber and asymmetric septal thickening, and these findings are noted in the Results section.

Measures of socioeconomic status were obtained by matching home addresses to the 1980 census tract data through the Chicago Area Geographic Information Study, Department of Geography of the University of Illinois at Chicago. Matches were achieved for 84.9% of patient addresses.

Cardiac catheterization: Hemodynamic data were collected from both right- and left-sided heart catheterization, and coronary cineangiograms were obtained in multiple projections. LV angiograms were obtained in the standard 30° right anterior oblique projection and the ejection fraction was calculated with the single plane method of Dodge. 13 Significant coronary artery disease was defined using the criterion of a >50% diameter reduction, and categorized as involving 1 to 3 major vessels. Left main stenosis was considered present with a >50% narrowing, and these patients were assigned 3vessel disease for the overall analysis. LV hypertrophy on the electrocardiogram was estimated using the computer programs available from Marquette Electronics,

Echocardiography: M-mode tracings were generated from the 2-dimensional echocardiogram using the

parasternal view in a 30° left lateral position. The leading edge to leading edge convention was used for estimates of cardiac dimensions according to standards of the American Society of Echocardiography. 14,15 Wall thickness was measured to the nearest 0.1 cm. LV mass was estimated by a modification of the Penn convention, as proposed by Devereux and Reichek16 and corrected to estimates based on autopsy studies<sup>17</sup>: LV mass = 1.05 [(LVIDD + IVS + LVPW) $^3$  - (LVIDD) $^3$ ]  $\times$ 0.80 + .6 g; where LVIDD = LV internal diastolic dimension (cm), IVS = ventricular septum and LVPW = diastolic posterior wall. Because of the correlation between height and LV mass observed in the normal population, 17,18 as well as our own data set (LV mass vs height, r = 0.3), the principal variable used to estimate the degree of LV hypertrophy was LV mass indexed to height (g/m); no important differences were noted when these analyses were repeated with observed LV mass as the study variable.

Follow-up procedures: An attempt was made to contact all patients either during an outpatient visit, by telephone or by review of medical records of clinic attendance. When patients were lost to follow-up by these procedures, the records of the Illinois Department of Public Health were searched for death certificates; finally, the database provided by the National Death Index was searched for all members of the original cohort.19 Patients who were not contacted and confirmed to be alive and who were not matched to a death certificate were considered alive as of the last date included in the National Death Index file, namely, December 31, 1987. During the follow-up period 105 patients underwent coronary bypass grafting.

Statistical analysis: Data were coded and entered into a computerized database and analyses were performed with programs available on SPSS - PC + (SPSS, Inc.) and BMDP. For analyses comparing 2 groups chi-square tests were used for dichotomous variables and 2-tailed t tests were applied to continuous variables. Multivariate survival analyses were carried out with the Cox regression model using the maximum partial likelihood ratio method.

#### RESULTS

Table I lists data on the universe of patients from which the analytic sample was drawn. Mortality among all patients with coronary artery disease was approximately 5%/year, and no differences could be detected between patients with 2- and 3-vessel disease. In univariate Cox regression analysis the standard predictors of mortality, including sex, LV ejection fraction and number of vessels stenosed were identified. In stepwise multivariate analysis only the 2 angiographic variables remained significant (p <0.01). In the analytic sample of 744 patients with complete data for all variables and a normal size left ventricle, death within the follow-up period was associated with the following baseline characteristics—age, sex, number of diseased coronary vessels and electrocardiographic LV hypertrophy (Table II). Modest differences in socioeconomic status were observed between patients who survived and those who died; however, these differences were only significant

TABLE IV Echocardiographic Left Ventricular Hypertrophy as a Predictor of Mortality: Univariate Analysis Including Patients with a Dilated Left Ventricle

Variables	Survivors (n = 843)	Decedents (n = 77)	p Value
LV mass actual (g)	$264 \pm 100$	309 ± 121	0.006
LV mass/height (g/m)	$157 \pm 58$	181 ± 69	0.000
Ventricular septal thickness (cm)	$1.17 \pm 0.27$	$1.23 \pm 0.30$	0.097
Systolic internal diameter (cm)	$3.31 \pm 0.94$	$3.76 \pm 1.20$	0.000
Diastolic internal diameter (cm)	$4.96 \pm 0.80$	$5.33 \pm 0.96$	0.000
Prevalence of ECG LVH* (%)	62	81	0.010
Prevalence of disproportionate	1.9	6.5	0.040
ventricular septal thickening (%)	)		

All ± data are mean ± standard deviation.

\* LV mass/height > 100 g/m for women and > 128 g/m for men
Abbreviations as in Table I.

TABLE V Cox Regression Analysis of Left Ventricular Hypertrophy as a Predictor of Mortality

Univariate	Chi-Square	p Value	
Age	4.24	0.04	Shirt And
Sex	5.71	0.02	
Race	0.18	0.68	
No. of Stenosed Vessels	9.77	0.00	
Ejection fraction	3.60	0.06	
LV mass*.†	6.20	0.01	
Ventricular septum	10.50	0.00	
Posterior wall	13.11	0.00	
	Improvement		Relative
Multivariate	Chi-Square	p Value	Risk
Multivariate  Model I	Chi-Square	p Value	Risk
	Chi-Square 6.10	p Value 0.01	Risk
Model I			
Model I No. of stenosed vessels	6.10	0.01	2.3
Model I No. of stenosed vessels LV mass	6.10	0.01	2.3
Model I No. of stenosed vessels LV mass Model II	6.10 9.03	0.01 0.00	2.3 2.1
Model I No. of stenosed vessels LV mass Model II No. of stenosed vessels	6.10 9.03 6.10	0.01 0.00 0.01	2.3 2.1 1.4
Model I No. of stenosed vessels LV mass Model II No. of stenosed vessels Ventricular septum	6.10 9.03 6.10	0.01 0.00 0.01	2.3 2.1 1.4

LV mass indexed to height (g/m)

LV mass, ventricular septum and posterior wall entered in sequential analyses Risk associated with 100-g/m increase. Risk associated with a 0.1-cm increase.

Abbreviations as in Table I.

for percent blue collar (p = 0.05). Only a slight, nonsignificant difference in ejection fraction remained in this sample from which patients with a dilated heart had been excluded. Patients with normal coronaries had a slightly smaller average LV mass compared to those with coronary artery disease (122  $\pm$  vs 110  $\pm$  46); this was also true for patients without a history of hypertension compared to those with it (112  $\pm$  42 vs 117  $\pm$  32).

The mean LV mass among patients who died in the follow-up period was significantly higher than among those who survived (p <0.01), as were the other indexes and wall thickness measures (Table III). LV mass and the septal/posterior wall thickness were 12 to 15% higher among patients who died (p <0.01), while no differences were observed in internal LV dimensions when patients with eccentric hypertrophy had been removed. LV hypertrophy on echocardiogram was present in half of the patients, and was significantly more common in patients who died. Additional analyses restricted only to blacks yielded essentially the same findings (data not

shown). As expected, this pattern of findings was more pronounced in the total cohort including patients with a

dilated LV cavity (Table IV).

To estimate the independent contribution of LV mass to survival, stepwise Cox regression analysis was performed (Table V). While age and sex were associated with higher mortality in an univariate fashion, their predictive value disappeared after control for the severity of coronary disease. From among the remaining descriptive and socioeconomic status variables only percent blue collar contributed discriminatory information to the model (p = 0.08). Measures of LV hypertrophy were associated with the largest chi-square values of any variable except number of stenosed vessels. A 100g/m increase in LV mass conferred a doubling of risk. The calculated variable LV mass was chosen a priori as the best single estimate of LV hypertrophy because it offered a global measure of the weight of the left ventricle. However, in separate stepwise regression analyses, using ventricular septal thickness or the thickness of the LV posterior wall, the predictive value of the echocardiographic variable increased substantially (Table V). (Measures of LV mass were allowed to enter in 3 separate regression models in conjunction with the number of coronary stenoses.) The slightly higher chi-square value associated with posterior wall measurement may, in large part, be an artifact of the sampling procedures; when patients with disproportionate septal thickening were reintroduced into the sample the chi-square values for the septum and posterior wall were identical (improvement chi-square 8.9 and 9.4, respectively).

The relations derived from the Cox regression analysis described above persisted when patients with an ejection fraction <50% were eliminated (p = 0.05; relative risk = 2.0) and in an analysis including all patients with a dilated left ventricle (data not shown). Additional analysis restricted to 105 patients with multivessel coronary artery disease who had undergone coronary bypass grafting demonstrated an equivalent relative risk for increased LV mass (1.9), which was of borderline statistical significance in this small subsample. Among the surgical patients LV mass was increased by 20.9% among those who died, compared to survivors, and this difference was significant (p <0.05). Finally, coding for the presence of surgical versus medical therapy in the Cox regression model did not alter the predictive significance

of LV mass.

#### DISCUSSION

The data presented here demonstrate a consistent pattern of higher death rates during follow-up among patients with LV hypertrophy diagnosed by echocardiography, and this risk was independent of angiographically defined coronary anatomy and systolic ventricular function. Both calculated LV mass and direct measures of the thickness of the ventricular septal and posterior LV wall were predictors of mortality. Based on relative risk estimates from regression analyses, while an increase in 1-vessel coronary stenosis was associated with a 50% increase in mortality, the presence of severe LV hypertrophy (as reflected in a 100 g/m increase in LV

mass) resulted in a doubling of risk. Additionally, to assess this risk clinically it would be possible to avoid calculations of LV mass and use the echocardiographic measurements of LV wall thickness directly. Thus, an increase from a thickness of 1.1 to 1.2 cm in either the ventricular septum or the posterior wall was associated with an approximately 2- to 7-fold increase in the risk

This study provides no information about the mechanism by which LV hypertrophy results in higher cardiovascular mortality. Cause of death data were insufficient to distinguish sudden from nonsudden death. This question would be particularly important among those patients with normal coronary arteries who died, and future investigations must focus particularly on the incidence of sudden death in this group. A high rate of ventricular arrhythmias has been reported among patients with LV hypertrophy<sup>20-23</sup> and coronary reserve has been shown to be reduced in LV hypertrophy.<sup>23</sup> Transient ischemia, particularly in subendocardial regions, may predispose patients with LV hypertrophy to sudden death. Greater loss of muscle mass at the time of myocardial infarction may also contribute to the high mortality in this group.24 Finally, a reduction in diastolic function is a well-described feature of LV hypertrophy and may precipitate heart failure or pulmonary edema. 10,25 Substantial evidence exists that survival among blacks with coronary artery disease diagnosed by the occurrence of an acute myocardial infarction26,27 or angiography28 is greatly reduced compared to whites. The data presented herein add further support to the poor survival among black patients with symptomatic coronary disease. A partial explanation may lie in the high prevalence of LV hypertrophy.

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# **Spontaneous Sustained Ventricular Tachyarrhythmias During Treatment** with Type IA Antiarrhythmic Agents

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Twenty-six patients who developed their first clinical episode of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) while taking type IA antiarrhythmic agents for more benign rhythm disturbances were rechallenged with the identical drug during electrophysiologic testing. Patients with these new drug-associated spontaneous ventricular arrhythmias often manifested a preexisting substrate for such arrhythmias: sustained VT or VF was induced in 65% of patients at baseline, and in 58% of patients when tested with their previously taken antiarrhythmic drug. Among those without inducible sustained ventricular arrhythmias in the drug-free state, 78% remained free of inducible sustained arrhythmias when tested with the same drug they had been taking at the time of the clinical arrhythmia. Even patients without a definable electrophysiologic substrate for sustained VT or VF remained at risk for arrhythmia recurrence if treated with alternative antiarrhythmic medications: 40% of such patients who continued to receive an antiarrhythmic agent different from that being administered when their clinical VT or VF occurred had recurrent spontaneous ventricular tachyarrhythmias during follow-up. Thus, patients with drug-associated clinical sustained ventricular tachycardias form a heterogenous group that should be evaluated individually and not empirically managed for a "proarrhythmic effect" simply by antiarrhythmic drug withdrawal or drug substitution.

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ntiarrhythmic agents have been implicated in the worsening of arrhythmias in 5 to 24% of treated patients.<sup>1,2</sup> However, the causal relation between drug and arrhythmia is often elusive and difficult to establish with certainty. Occasionally, a patient taking an antiarrhythmic medication for a presumably benign rhythm abnormality (isolated ventricular premature complexes or atrial dysrhythmias) subsequently develops sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) during such treatment. Is it appropriate to presume that the drug was the cause of this new sustained arrhythmia? Is the patient optimally managed by strict avoidance of the offending drug? If the original indication for antiarrhythmic drug therapy persists, what alternative drugs can be used safely? To answer such questions, this study focused on a patient population with no previous documented sustained ventricular arrhythmias who experienced their first such sustained arrhythmia during treatment with antiarrhythmic medications.

#### **METHODS**

Patients: We evaluated 26 consecutive patients (19 men and 7 women), 62.8 ± 9.7 years of age (range 43 to 78) who developed their first documented clinical episode of spontaneous sustained VT (18 patients) or VF (8 patients) while taking procainamide, quinidine or disopyramide. These spontaneous arrhythmias required acute therapeutic intervention in all patients.

Seven of these 26 patients (27%) had received antiarrhythmic treatment primarily for control of isolated ventricular premature complexes. Twelve patients (46%) were being treated for narrow complex atrial tachyarrhythmias (atrial fibrillation, atrial flutter or nodal reciprocating tachycardia). Three patients (12%) were receiving antiarrhythmic agents for palpitations without clearly documented arrhythmias. One patient (4%) was treated for syncope of unknown etiology and 1 patient was being treated for nonsustained ventricular tachycardia. Two patients (8%) had been taking antiarrhythmic drugs for indications that were unclear at the time of their referral. No patient had experienced previous clinical sustained VT or VF, no patient had a myocardial infarction within 3 months of the arrhythmia event and no patient had QT prolongation in the drugfree state or evidence of preexcitation (Table I).

Plasma concentrations of antiarrhythmic medications were not available in most patients from the time of their clinical sustained arrhythmias. One patient ex-

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TABLE I Clinical Characteristics, Results of Electrophysiologic Testing, Treatment and Outcome Among Patients with Drug-Associated Sustained Clinical Ventricular Tachycardia or Fibrillation

Age (yrs),		Age (vrs).		Historical	Drug- Related	Electrophysiologic Testing		Long-Term	Clinical Outcome	
	Arrhythmia	LVEF			On Drug*	Treatment	Alive	VT		
Procair		ated clinical V	T/VF	THE BANK		ALL PRINT				AND THE PARTY
1	54, M	CAD	Palpitations	0.20	VF	1-3 VPCs	7-9 VPCs	0	+	0
2	50, M	CAD	AFlut	Normal	VT	VT	VT	0	+	+
3	74, M	Normal	AFlut	0.34	VT	VF	VF	Quinidine	+	+
4	67, M	CAD	VPCs	Normal	VF	VT	VT	Phenytoin	0	(SD)
5	67, M	CAD	PAT	0.40	VT	VT	VT	Amiodarone	+	+
6	78, M	CAD	Palpitations	0.46	VT	VT	VT	Amiodarone	+	+
7	56, M	CM	VPCs	0.21	VT	VF	VT	Amiodarone	+	+
		clinical VT/VF								
8	60, F	SH	AFib	Normal	VF	1-3 VPCs	1-3 VPCs	.0	+	0
9	60, F	Normal	AFib	Normal	VT	1-3 VPCs	1-3 VPCs	0	+	0
10	73, F	CAD	AFib	Normal	VT	1-3 VPCs	1-3 VPCs	0	+	0
11	43, M	CAD	AFib	Normal	VF	4-6 VPCs	4-6 VPCs	Procainamide	+	+
12	59, F	CAD	AFib	0.53	VF	7-9 VPCs	4-6 VPCs	Phenytoin	+	0
13	63, M	CAD	VPCs	0.17	VT	7-9 VPCs	4–6 VPCs	Phenytoin	+	+
14	60, M	CM	AFib	0.24	VF	7-9 VPCs	4–6 VPCs	Amiodarone	+	0
15	49, M	CAD	VPCs	Abnl	VT	VT	VT	Procainamide	+	0
16	62, M	CAD	PAT	0.37	VT	VF	VT	Procainamide	0	(SD)
17	65, M	CAD	Unclear	0.41	VF	VF	1-3 VPCs	Procainamide	+	0
18	73, M	CAD	VPCs	0.29	VT	VT	4–6 VPCs	Procainamide	+	0
19	60, F	CM	PAT	0.69	VT	VF	1-3 VPCs	Disopyramide	+	0
20	49, M	CAD	VPCs	Abnl	VF	VF	VF	Amiodarone	+	0
21	56, M	CAD	VPCs	0.36	VT	VT	VT	Amiodarone	0	(SD)
22	78, M	CAD	Unclear	Abnl	VT	VT	VT	Amiodarone	0	(SD)
Disopyr	amide-associa	ated clinical VI	/VF					a moder one		(30)
23	59, M	CAD	Syncope	Normal	VT	4-6 VPCs	VT	Phenytoin	+	0
24	64, F	CAD	NSVT	0.46	VT	VT	VT	Procainamide	+	0
25	62, M	CAD	Palpitations	0.40	VT	VT	VT	Procainamide	0	0
26	65, F	CAD	PAT	0.45	VT	VT	VT	Amiodarone	+	0

Patients were grouped by the drug taken at the time of their clinical arrhythmia and by the results of drug-free electrophysiologic testing.

\* During treatment with the antiarrhythmic drug associated with the patient's clinical sustained arrhythmia.

Abril = moderately to severely diminished; AFib = atrial fibrillation; AFlut = atrial flutter; CAD = coronary artery disease; CM = cardiomyopathy; NSVT = nonsustained ventricular schycardia; VPCs = ventricular premature complexes; SH = systemic hypertension; VT = ventricular tachycardia; VF = ventricular fibrillation;

perienced spontaneous sustained ventricular arrhythmia after the first dose of quinidine sulfate. All other patients had been taking stable doses of antiarrhythmic medications for at least 1 week before their clinical sustained arrhythmia. Concentrations of serum electrolytes were normal in all but 1 patient, whose potassium concentration was 2.5 mEq/liter at the time of the clinical event. Concentrations of digoxin were within normal limits (<2 ng/ml) in all patients taking digitalis preparations.

Clinical evaluation: Before electrophysiologic study, a quantitative measure of left ventricular function (ejection fraction) was obtained by either contrast or radionuclide ventriculography in 16 of 26 patients (62%), and averaged (mean ± standard deviation) 38 ± 13% (range 17 to 69). In the remaining 10 patients, a qualitative assessment of left ventricular function was normal in 7 patients, and moderately to severely depressed in 3

Electrophysiologic evaluation: All patients underwent an identical electrophysiologic evaluation, consisting of 2 baseline, drug-free electrophysiologic studies, 6 to 24 hours apart, followed by serial drug testing. This

protocol had been approved by the human subjects review committee at the Oregon Health Sciences University, and informed consent was obtained from patients before study.

All antiarrhythmic agents were discontinued for at least 4 half-lives before the first programmed electrical stimulation. Our stimulation protocol has been previously reported,3,4 and included decremental pacing followed by programmed pacing from the right ventricle using up to 4 extrastimuli. Stimulation was terminated on the induction of a sustained ventricular tachyarrhythmia, or on completion of the entire stimulation protocol through 4 ventricular extrastimuli. Drug testing followed an identical stimulation protocol.

Serial antiarrhythmic drug trials: All patients were specifically tested at therapeutic plasma concentrations of the antiarrhythmic medication taken at the time of their clinical event. If tolerated, all patients were also tested with a variety of other antiarrhythmic agents (procainamide, quinidine, disopyramide and phenytoin) at therapeutic plasma concentrations. The newer antiarrhythmic agents were not routinely available or being tested at the time these patients were evaluated.

During serial electrophysiologic studies, any previously administered antiarrhythmic agents were discontinued for at least 4 half-lives before study of a new drug. This was confirmed by the absence of measurable plasma concentrations of any previously given medication at the time of electrophysiologic testing. Any medical illness or the presence of clinical congestive heart failure was controlled before such testing. No patient underwent surgery or sustained a myocardial infarction between serial electrophysiologic trials. Patients taking other cardiac medications at the time of their clinical arrhythmia were maintained on identical doses of such agents during all studies.

Rhythms induced during programmed electrical stimulation: Sustained VT: VT lasting >30 seconds or requiring intervention.

VF: completely disorganized electrical activity on all surface leads necessitating therapeutic intervention.

Monomorphic VT: VT manifesting a uniform, single QRS configuration in each of at least 3 surface electrocardiographic leads.

Polymorphic VT: VT manifesting >1 QRS configuration within any recorded surface electrocardiographic lead

RHYTHM EVALUATION: Tracings of patients' clinical sustained VT were frequently available in at most only 1 electrocardiographic lead. Therefore, precise comparison of rhythm configurations induced in the electrophysiologic laboratory with those having occurred clinically could not be consistently performed. The results of the 2 drug-free tests were not always reproducible.<sup>3</sup> In such instances, the worst rhythm induced in the 2 drug-free studies was compared to rhythms induced during drug testing. The conclusions of this study were un-

changed when data were reanalyzed excluding the 7 patients (27%) whose arrhythmias were not reproducible from day to day.

Follow-up: Patients were followed for a mean of 14.5 ± 14 months (range 1 to 57 months) after hospital discharge. Any symptomatic episodes consistent with arrhythmia recurrence were evaluated by Holter monitoring or by in-hospital telemetry monitoring. Patients were judged to have recurrent arrhythmias if, at time of follow-up, they had documented clinical episodes of sustained ventricular tachyarrhythmias or symptomatic nonsustained VT of >10 beats duration. Any otherwise unexplained deaths occurring within 1 hour of symptom onset were regarded as probable sudden cardiac death due to a recurrent arrhythmia. Arrhythmia-free survival denoted a patient being alive and free of recurrent arrhythmias at follow-up.

**Statistical analysis:** Statistical analysis was performed using a 2-tailed Student t test, chi-square or Fisher's exact test. Breslow and Mantel-Cox analyses were used to evaluate life tables of adverse events during follow-up. A p value >0.10 was defined as insignificant.

#### RESULTS

A high frequency of inducible sustained ventricular tachyarrhythmias was observed among patients with drug-associated spontaneous arrhythmias, even in the drug-free state (Figure 1). Seventeen of 26 patients (65%) had inducible sustained VT or VF in the drug-free state during programmed stimulation. Sustained ventricular arrhythmias were more frequently induced among patients with abnormal left ventricular function (ejection fraction <50% or qualitatively described as

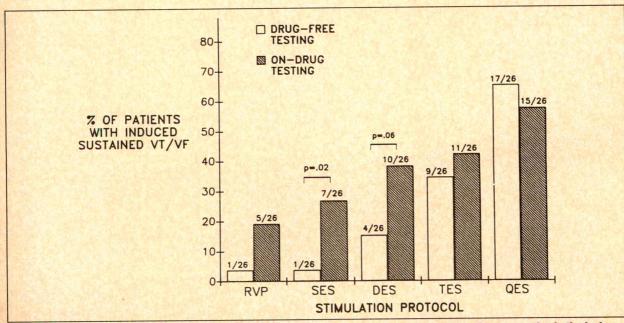


FIGURE 1. Results of drug-free electrophysiologic testing (white columns) and results of testing the same antiarrhythmic drug that patients were taking during their clinical event (hatched columns). DES = double programmed extrastimuli; QES = quadruple programmed extrastimuli; RVP = rapid ventricular pacing; SES = single programmed extrastimulus; TES = triple programmed extrastimuli; VT/VF = ventricular tachycardia or fibrillation.

"depressed") than among patients with normal or nearnormal (ejection fraction  $\geq 50\%$ ) ventricular function (82 vs 33% of patients, respectively, p <0.02). Whether the clinical arrhythmia had occurred during treatment with quinidine, procainamide or disopyramide did not significantly change the observed frequency of induced sustained tachyarrhythmias in the drug-free state (p >0.16) (Table I).

Serial drug testing: A sustained ventricular tachyarrhythmia was induced in 15 of 26 patients (58%) when testing the same antiarrhythmic drug taken at the time of their clinical spontaneous arrhythmia. This induction rate was comparable to the proportion of these patients who had inducible tachyarrhythmias in the drug-free state (65%, p >0.4, Figure 1). The configuration of the tachycardia was monomorphic in 12 of the 15 patients (73%) with inducible sustained VT during drug-testing, compared to 10 of 17 patients (58%) in the drug-free state (p >0.18).

Among 9 patients without inducible sustained VT or VF in the drug-free state, such rhythms remained non-inducible in 7 of these 9 patients (78%) when tested with the same drug they had been taking at the time of their clinical arrhythmia. Among 17 patients with inducible sustained ventricular tachyarrhythmias in the drug-free state, such rhythms remained inducible in 14 of 17 patients (82%) when tested with the same drug taken at the time of their spontaneous arrhythmia event. Among patients with inducible sustained ventric-

ular arrhythmias in the drug-free state and who remained persistently inducible during drug therapy, the addition of their previously taken antiarrhythmic agent frequently slowed the rate of the induced tachycardia (7 of 14 patients [50%]), and was never observed to significantly accelerate the rate of the induced tachycardia.

Stimulation protocol: Compared to drug-free electrophysiologic testing, to provoke sustained VT or VF during testing of their previously taken antiarrhythmic drug, 7 patients (47%) required a greater number of extrastimuli, 2 patients (13%) required an equal number of extrastimuli and 6 patients (40%) required fewer extrastimuli.

With a single or double extrastimulus protocol, sustained VT or VF was induced more frequently when patients were tested with their previous antiarrhythmic medication than when tested in the drug-free state (p = 0.02, p = 0.06, respectively) (Figure 1). This difference in the ability to induce sustained VT or VF during programmed stimulation thereafter diminished with each added extrastimulus. Thus, if proarrhythmia were judged by a higher frequency of inducible sustained VT in the setting of drug treatment, its presence was most strongly supported by the response to up to 2 programmed extrastimuli, and was less apparent after greater numbers (>2) of extrastimuli (p >0.3).

Induction rates and initial indications for drug therapy: Compared to their own baseline test results, patients with a history of only supraventricular arrhyth-

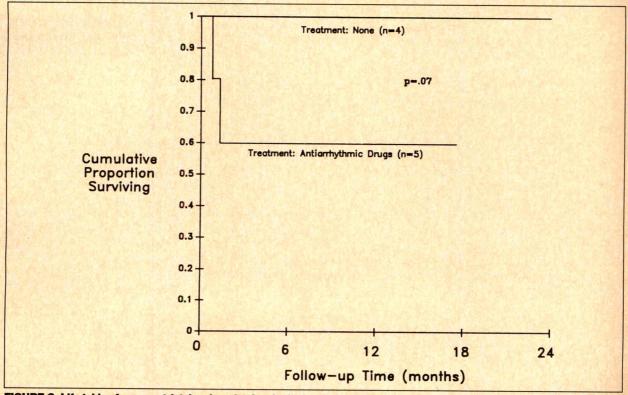


FIGURE 2. Life table of recurrent fatal and nonfatal arrhythmias during follow-up in patients without inducible sustained ventricular arrhythmias during drug-free electrophysiologic testing and who were not subsequently treated with antiarrhythmic drugs, compared to patients without inducible sustained ventricular arrhythmias who were treated with antiarrhythmic drugs.

mias (supraventricular tachycardia, atrial fibrillation and atrial flutter) rechallenged with their previously taken antiarrhythmic medication did not appreciably change their frequency of inducible sustained ventricular arrhythmias during programmed stimulation (50 vs 42% of patients, p = 0.5) any more so than for patients initially treated for indications other than supraventricular tachycardia (79 vs 71% of patients, p = 0.5) (Table I). That is, among this select group, the risks (as determined by inducibility during electrophysiologic testing) of having given an antiarrhythmic drug to a patient with a seemingly "more benign" versus potentially "serious" initial clinical rhythm disturbance seemed to be comparable.

Patient follow-up: Patients were selected for longterm antiarrhythmic drug therapy based on the results of electrophysiologic study and clinical indications. The decision to treat patients was not prospectively designed and rested on 2 factors: concerns over untreated inducible sustained VT or VF in the drug-free state and an ongoing need for arrhythmia prophylaxis among patients with supraventricular tachycardias or symptomatic ventricular premature complexes. When treated, patients received the agent found to prevent either the induction of sustained VT or VF or a symptomatic nonsustained ventricular tachycardia of >10 beats duration during serial electrophysiologic testing. Failure to achieve such control resulted in treatment with amiodarone. Other than during electrophysiologic testing, no patients were treated long-term with the same drug they were taking when their clinical sustained arrhythmia had taken place.

Treatment and outcome during patient follow-up are listed in Table I. Among patients without inducible ventricular tachyarrhythmias during drug-free testing, 40% of those subsequently treated with antiarrhythmic agents had recurrent VT during follow-up. Half of patients who were treated for inducible VT or VF during drug-free testing also had recurrent ventricular tachyarrhythmias during follow-up; 25% of such treated patients died suddenly. Among all patients treated with amiodarone, 63% had recurrent ventricular tachyarrhythmias; 25% died suddenly. Lifetable analyses were performed, evaluating 3 possible adverse outcomes during follow-up: sudden cardiac death, recurrent fatal or nonfatal VT or VF and deaths from all causes. There were no statistically significant differences in any of these clinical outcomes (1) whether patients had inducible sustained ventricular arrhythmias during baseline electrophysiologic testing (p >0.2), (2) whether left ventricular function was near normal (ejection fraction >50% or qualitatively described as normal) versus depressed (p >0.5) and (3) regardless of the clinical rhythm abnormality that initially prompted antiarrhythmic treatment (p >0.7). Patients who had no inducible sustained ventricular arrhythmias during drugfree programmed stimulation and who were not subsequently treated with antiarrhythmic drugs had a higher survival free of recurrent fatal and nonfatal VT than patients without inducible VT or VF at baseline, but

who were thereafter treated with antiarrhythmic drugs (100 vs 60%, respectively, p = 0.07) (Figure 2).

#### DISCUSSION

The ability to incriminate a particular drug as causing an adverse arrhythmia depends on the patient population selected<sup>5,6</sup> and the method chosen to implicate the presence of a proarrhythmic drug effect.<sup>2,7</sup> This study focused on a patient population with no previous documented sustained ventricular tachyarrhythmias. Most patients had structural heart disease and were treated chronically with moderate doses of type IA antiarrhythmic agents. The presence of a proarrhythmic drug effect was assessed by invasive electrophysiologic study.

Previous studies of proarrhythmic drug effects have been primarily performed among patients with a history of complex ventricular ectopy (nonsustained and sustained VT) before drug treatment. For example, among 8 survivors of cardiac arrest who had been treated with antiarrhythmic drugs for a previous history of nonsustained VT, Ruskin et al8 were not able to induce any sustained ventricular tachyarrhythmias during programmed stimulation in the drug-free state. However, during treatment with the drug associated with the clinical arrest, 6 of 8 patients (75%) were inducible to sustained VT or VF. Among this selected group of patients, treatment with antiarrhythmic drugs appeared to provoke a sustained arrhythmia that might not otherwise have occurred. A variety of presumably proarrhythmic effects has also been reported during antiarrhythmic drug trials directed by programmed stimulation. In their study of 160 patients who underwent electrophysiologic testing for sustained and nonsustained ventricular tachyarrhythmias not associated with antiarrhythmic drugs, Rae et al9 identified potentially proarrhythmic effects in 68 of 432 drug trials (16%).

The findings of the present study differ from these previous reports. Although their first clinical sustained ventricular arrhythmia occurred in the setting of drug therapy, the majority of our patients were found to have inducible sustained VT or VF even in the drug-free state. Moreover, the addition of antiarrhythmic drug therapy, including the drug taken at the time of the clinical arrhythmia, neither increased the overall frequency of inducible sustained ventricular tachyarrhythmias during programmed stimulation among such patients, nor accelerated the rate in those identified to have VT. If a potential proarrhythmic drug effect was present in this group of patients, its demonstration was limited to an apparent greater ease of inducing sustained VT or VF in response to 1 or 2 programmed extrastimuli during drug therapy. This phenomenon was less apparent after greater numbers of extrastimuli. The ability to demonstrate a proarrhythmic effect during electrophysiologic stimulation may therefore depend on the aggressiveness of the stimulation protocol used during drug-free and drug testing.

Patients with drug-associated spontaneous VT or VF remain at risk for recurrent clinical ventricular tachyarrhythmias unrelated to continued challenge with

the same drug. In the present study, 2-year arrhythmiafree survival appeared to be highest (100%) among patients without inducible sustained arrhythmias during drug-free electrophysiologic testing, and who were not subsequently treated with such drugs. It was lower among treated patients with versus without inducible sustained ventricular arrhythmias when drug-free (50 vs 60%, respectively), and lowest (37%) among patients requiring treatment with amiodarone, the majority of whom had persistently inducible ventricular arrhythmias during treatment with other agents. Comparable survival data have been reported among other patients with malignant sustained VT treated with conventional antiarrhythmic agents or amiodarone. 10-16

Implications: Patients with drug-associated spontaneous ventricular tachyarrhythmias are a heterogenous group. In some patients, drug therapy may simply coincide with the appearance of a sustained ventricular tachyarrhythmia whose substrate was already present. The presumed proarrhythmic drug may be an innocent bystander and not a participant in the arrhythmia event at all. Such patients frequently have inducible sustained VT or VF even in the drug-free state and may, accordingly, remain at high risk for recurrent spontaneous arrhythmia episodes.

In other patients with drug-associated spontaneous ventricular arrhythmias, drug-free electrophysiologic testing may fail to identify a basis for sustained ventricular tachyarrhythmias. Among such individuals, drug therapy may genuinely adversely alter their arrhythmia substrate in a manner not necessarily predictable by electrophysiologic testing. The risk of continued challenge with antiarrhythmic drugs in such patients should be balanced against the clinical indication for antiarrhythmic therapy.

Thus, when an antiarrhythmic medication is associated with a new sustained ventricular arrhythmia, simply discontinuing the presumed offending drug or empirically treating such patients with an alternative antiarrhythmic agent does not necessarily diminish the risk of arrhythmia recurrence. In fact, continued challenge even with alternative antiarrhythmic agents among patients with drug-associated spontaneous sustained ventricular arrhythmias may be potentially dangerous. Patients with an ongoing need for such treatment should, perhaps, be considered for the added protection of an implanted antitachycardia device.

Limitations: This study was performed among a select group of patients who had been treated with type IA antiarrhythmic drugs for relatively benign rhythm disturbances at the time of their clinical sustained arrhythmia. It does not address those patients with known previous sustained or nonsustained VT, or previous cardiac arrest, nor does it necessarily apply to therapy with newer classes of antiarrhythmic drugs.

Plasma antiarrhythmic drug concentrations and 12lead electrocardiograms from the time of patients' clinical arrhythmias were infrequently available from referral sources during this study. However, previous studies have not documented a meaningful correlation between

plasma antiarrhythmic drug concentrations or 12-lead electrocardiographic interval characteristics and the occurrence of a proarrhythmic effect. 17,18

The optimal stimulation protocol during multiple drug testing remains controversial. Previous work has demonstrated that use of 3 or 4 extrastimuli is not necessarily inappropriate for patients with a history of clinical sustained VT or VF.19 While it is possible that our inability to suppress rhythm induction with drugs was due to use of up to 4 programmed extrastimuli,20 others have argued to the contrary that drug trials may be incorrectly interpreted as suppressing the induction of ventricular tachyarrhythmias if more complex methods of programmed stimulation are not used. 21,22 For those wishing to study the ability to induce sustained VT or VF among such patients with fewer extrastimuli, we also analyzed results of programmed stimulus protocols using lesser numbers of extrastimuli (Figure 1). Although the absolute numbers of patients identified to have sustained ventricular arrhythmias would change when fewer programmed extrastimuli are used, the overall conclusions of this investigation would remain unaltered.

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Professor of Internal Medicine Chief, Hypertension Division University of Texas Southwestern Medical Center at Dallas Dallas, Texas

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Norman K. Hollenberg, MD, PhD

Discussion

What is the Clinical Impact of Insulin Resistance as a Risk Factor?

Ralph A. DeFronzo, MD

Discussion

Does Hypertension Contribute to the Atherosclerotic Process and Can it be Prevented?

Aram V. Chobanian, MD

Discussion

Antihypertensive Agents and Risk Factors: Does Choice of Therapy Make a Difference?

Henry R. Black, MD

Discussion

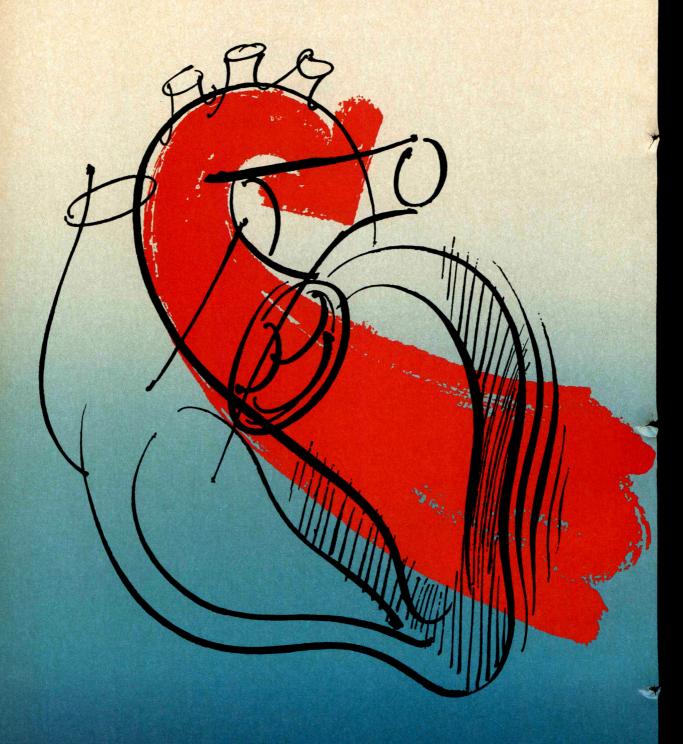
Hypertension Management: How Can We Maximally Reduce Cardiovascular Risk?

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Discussion

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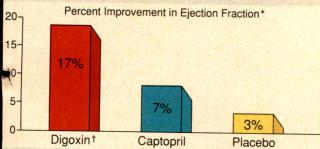
# New evidence continues to confirm the essential value of LANOXIN® in CHF.<sup>1,2</sup>



# Improved ejection fraction

In a recent double-blind, placebo-controlled study in patients with normal sinus rhythm, digoxin produced a significant increase in ejection fraction compared to captopril (P<.05) and placebo (P<.01). By contrast, there was no significant difference between captopril and placebo.

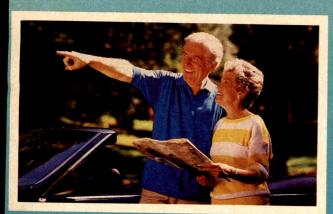
Improvement in ejection fraction represents improvement in myocardial contractile performance and better emptying of the left ventricle.



\* Adapted from the Captopril-Digoxin Multicenter Research Group study. 
† P<.05 compared to captopril; P<.01 compared to placebo.

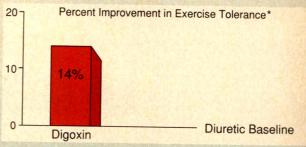
## Improved cardiac output

The positive inotropic effect of digoxin (as measured in part by improved cardiac output) was associated with improved left ventricular (LV) function. This significant improvement in cardiac output was seen in patients at rest as well as during exercise. Long-term therapy with digoxin contributed to the maintenance of LV function as indicated by both a decrease in cardiac output when digoxin was stopped and a restoration treatment levels with readministration of the drug.



# Improved exercise tolerance

In a new placebo-controlled study<sup>2</sup> of CHF patients with normal sinus rhythm and on diuretics, exercise tolerance (treadmill) was improved 14% (P<.05) by digoxin. In this study, digoxin produced favorable effects on cardiac function beyond those of the diuretic alone. Another study<sup>4</sup> showed that digoxin significantly improved exercise tolerance and  $O_2$  consumption over placebo. In the latest digoxin/captopril study, there was no significant statistical difference between the two drugs with regard to effects on exercise tolerance and functional class.<sup>1</sup>



\* Adapted from DiBianco et al.2

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LANOXIN®
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Unique inotropic support for the failing heart.

See brief summary of prescribing information on following page.

ANOXIN® (DIGOXIN) TABLETS

µg (0.125 mg) Scored I.D. Imprint Y3B (yellow)

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µg (0.5 mg) Scored I.D. Imprint T9A (green)

ore using Lanoxin Tablets, the physician should be thoroughly familiar with basic pharmacology of this drug as well as its drug interactions, indications,

RIPTION: Lanoxin is digoxin, one of the cardiac (or digitalis) glycosides, a closely related group of drugs having mmon specific effects on the myocardium.

CATIONS AND USAGE:

IF Failure: The increased cardiac output resulting from the inotropic action of digoxin ameliorates the distur-se characteristic of heart failure (venous congestion, edema, dyspnea, orthopnea and cardiac asthma). kin is more effective in "low output" (pump) failure than in "high output" heart failure secondary to arteriovenous

ixin is more effective in 'low output' (pump) failure than in 'high output' near trailure seculidar y ut at teriovenuda a, anemia, infection or hyperthyroidism. 
ixin is usually continued after failure is controlled, unless some known precipitating factor is corrected. Studies shown, however, that even though hemodynamic effects can be demonstrated in almost all patients, corressing improvement in the signs and symptoms of hear trailure is not necessarily apparent. Therefore, in patients in midigoxin may be difficult to regulate, or in whom the risk of toxicity may be great (e.g., patients with unstable I function or whose potassium levels tend to fluctuate) a cautious withdrawal of digoxin may be considered. If xin is discontinuation dependent, and understand effect requiring permanent discontinuation of other digitalis preparations usually given patient, an untoward effect requiring permanent discontinuation of other digitalis preparations usually stitutes a contraindication to digoxin. Hypersensitivity to digoxin itself is a contraindication to its use. Allergy to xin, though rare, does occur. It may not extend to all such preparations, and another digitalis glycoside may be with caution.

I with caution.

RNINGS: Digitalis alone or with other drugs has been used in the treatment of obesity. This use of digoxin or other alis glycosides is unwarranted. Moreover, since they may cause potentially fatal arrhythmias or other adverse tst, the use of these drugs solely for the treatment of obesity is dangerous. The treatment of the cause of these symptoms should be attempted before further digitalis initistration. In such circumstances determination of the serum digoxin concentration may be an aid in deciding ther or not digitalis toxicity is likely to be present. If the possibility of digitalis intoxication cannot be excluded, lac glycosides should be temporarily withheld, if permitted by the cal situation.

ents with renal insufficiency require smaller than usual maintenance as of digoxin (see DOSAGE AND ADMINISTRATION section in the com-

prescribing information).
failure accompanying accompanyi mpanying acute glomerulonephritis requires extreme care talization. Relatively low loading and maintenance doses and concomises of antihyper tensive drugs may be necessary and careful monitoring ential. Digoxin should be discontinued as soon as possible.

Its with severe carditis, such as carditis associated with rheumatic

ints with severe carditis, such as carditis associated with rheumatic or viral myocarditis, are especially sensitive to digoxin-induced distur-

ces of rhythm. Wobern infants display considerable variability in their tolerance to digox-Premature and immature infants are particularly sensitive, and dosage st not only be reduced but must be individualized according to their

: Digitalis glycosides are an important cause of accidental poisoning in

Burrough
meral: Digoxin toxicity develops more frequently and lasts longer in
meral: Digoxin toxicity develops more frequently and lasts longer in
meral: Digoxin toxicity develops more frequently and lasts longer in
meral: It should be anticipated that dosage requirements will be
reased in patients with moderate to severe renal disease (see DOSAGE
D ADMINISTRATION section in the complete prescribing information,
cause of the prolonged half-life, a longer period of time is required to
nieve an initial or new steady-state concentration in patients with renal
pairment than in patients with normal renal function.
patients with hypokalemia, toxicity may occur despite serum digoxin
neentrations within the "normal range", because potassium depletion
neitizes the myocardium to digoxin. Therefore, it is desirable to maintain
rmal serum potassium levels in patients being treated with digoxin. Hypokalemia may result from diuretic,
hypotaricin B or corticosteroid therapy, and from dialysis or mechanical suction of gastrointestinal secretions. It
by also accompany malnutrition, diarrhea, prolonged vomiting, old age and long-standing heart failure. In general,
old changes in serum potassium or other electrolytes should be avoided, and intravenous treatment with potassium
old be reserved for special circumstances as described below (see TREATMENT OF ARRHYTHMIAS PRODUCED

OVERDOSAGE section).

OVERDUSAGE section).

gium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in tailized patients. Hypercalcemia from any cause predisposes the patient to digitalis toxicity. On the other hand, localcemia can nullify the effects of digoxin in man; thus, digoxin may be ineffective until serum calcium is restored normal. These interactions are related to the fact that calcium affects contractility and excitability of the heart in a

normal. These interactions are related to the fact that calcium affects contractility and excitability of the heart in a anner similar to digoxin.

promagnesemia may predispose to digitalis toxicity. If low magnesium levels are detected in a patient on digoxin, placement therapy should be instituted.

inidine, verapamil, and amidodarone cause a rise in serum digoxin concentration, with the implication that digitalis toxication may result. This rise appears to be proportional to the dose. The effect is mediated by a reduction in the goal in the case of quinidine, decreased volume of distribution as well.

In the case of quinidine, decreased volume of distribution as well.

In antibiotics may increase digoxin absorption in patients who convert digoxin to inactive metabolites in the guere Pharmacokinetics portion of the CLINICAL PHARMACOLOGY section in the complete prescribing information), seent studies have shown that specific colonic bacteria in the lower gastrointestinal tract convert digoxin to indicionactive reduction products, thereby reducing its bioavailability. Although inactivation of these bacteria by hibibitics is rapid, the serum digoxin concentration will rise at a rate consistent with the elimination afficited or goxin. The magnitude of rise in serum digoxin concentration relates to the extent of bacterial inactivation, and may as much as two-fold in some cases. Patients with acute myocardial infarction or severe pulmonary disease may be as much as two-fold in some cases. Patients with acute myocardial infarction or severe pulmonary disease may be as much as two-fold in some cases.

as much as two-fold in some cases. Patients with acute myocardial infarction or severe pulmonary disease may be usually sensitive to digoxin-induced disturbances of rhythm. 
It is a rhythmias associated with hypermetabolic states (e.g. hyperthyroidism) are particularly resistant to digoxin 
atment. Large doses of digoxin are not recommended as the only treatment of these arrhythmias and care must be 
en to avoid toxicity if large doses of digoxin are required. In hypothyroidism, the digoxin requirements are 
fuced. Digoxin responses in patients with compensated thyroid disease are normal, 
duction of digoxin dosage may be desirable prior to electrical cardioversion to avoid induction of ventricular 
hythmias, but the physician must consider the consequences of rapid increase in ventricular response to atrial 
rillation if digoxin is withheld 1 to 2 days prior to cardioversion. If there is a suspicion that digitalis toxicity exists, 
ctive cardioversion should be delayed. If it is not prudent to delay cardioversion, the energy level selected should 
minimal at first and carefully increased in an attempt to avoid precipitating ventricular arrhythmias. 
somplete AV block, especially in patients with Stokes-Adams attacks, may progress to advanced or complete heart 
well indigoxin is given.

ck if digoxin is given. some patients with sinus node disease (i.e. Sick Sinus Syndrome), digoxin may worsen sinus bradycardia or sino-

rial block.

patients with Wolff-Parkinson-White Syndrome and atrial fibrillation, digoxin can enhance transmission of publises through the accessory pathway. This effect may result in extremely rapid ventricular rates and even intricular fibrillation.

goxin may worsen the outflow obstruction in patients with idiopathic hypertrophic subaortic stenosis (IHSS), niess cardiac failure is severe, it is doubtful whether digoxin should be employed.

attents with chronic constrictive pericarditis may fail to respond to digoxin. In addition, slowing of the heart rate by goxin in some patients may further decrease cardiac output.

titents with heart failure from amyloid heart disease or constrictive cardiomyopathies respond poorly to treatment this digoxin.

Digoxin is not indicated for the treatment of sinus tachycardia unless it is associated with heart failure.

Digoxin may produce false positive ST-T changes in the electrocardiogram during exercise testing.

Intranuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration

Laboratory Tests: Patients receiving digoxin should have their serum electrolytes and renal function (BUN and/or serum creatinine) assessed periodically: the frequency of assessments will depend on the clinical setting. For discussion of serum digoxin concentrations, see DOSAGE AND ADMINISTRATION section in the complete prescribing

discussion of serum digoxin concentrations, see DUSAGE AND ADMINISTRATION section in the complete prescribing information.

Drug Interactions: Potassium-depleting corticosteroids and diuretics may be major contributing factors to digitalis toxicity. Calcium, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Quinidine, verapamil, and amiodarone cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. Certain ambibidics increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result. Propantheline and diphenoxylate, by decreasing gut motility, may increase digoxin absorption. Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine and certain anticance drugs may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. There have been inconsistent reports regarding the effects of other drugs on the serum digoxin. Concomitant use of digoxin and sympathomimetics increases the risk of cardiac arrhythmias because both enhance ectopic pacemaker activity. Succinylcholine may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although 8 adrenergic blockers or calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in complete heart block.

Due to the considerable variability of these interactions, digoxin dosage should be carefully individualized when patients receive coadministered medications.

Carlingenesis, Mutagenesis, Impairment of Fertility: There have been no long-term studies performed in animals to evaluate carcinogenic potential.

evaluate carcinogenic potential.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with digoxin. It is also not known whether digoxin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Digoxin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Studies have shown that digoxin concentrations in the mother's serum and milk are similar. However, the estimated daily dose to a rursing infant will be far below the usual infant maintenance dose. Therefore, this amount should have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when digoxin is administered to a rursing woman.

ADVERSE REACTIONS: The frequency and severity of adverse reactions to disavis described to disavis described to the control of the contro

administered to a nursing woman.

ADVERSE REACTIONS: The frequency and severity of adverse reactions to digoxin depend on the dose and route of administration, as well as on the patient's underlying disease or concomitant therapies (see PRECAUTIONS section). The overall incidence of adverse reactions has been reported as 5 to 20%, with 15 to 20% of them being considered serious (one to four percent of patients receiving digoxin). Evidence suggests that the incidence of toxicity has decreased since the introduction of the serum digoxin assay and improved standardization of digoxin tablets. Cardiac toxicity accounts for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverses reactions.

cicity for about one-fourth of these adverse reaction

IN THE EARLY TREATMENT OF CHE

(digoxin) Tablets

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LANOXI

Cardiac-Unifocal or multiform ventricular premature contractions

Cardiac—Unifocal or multiform ventricular premature contractions, especially in bigeninal or trigeminal patterns, are the most common arrhythmias associated with digoxin toxicity in adults with heart disease. Ventricular tachycardia may result from digitalis toxicity. Atrioventricular clav) dissociation, accelerated junctional (nodal) rhythm and atrial tachycardia with block are also common arrhythmias caused by digoxin overdosage. Excessive slowing of the pulse is a clinical sign of digoxin overdosage. AV block (Wenckebach) of increasing degree may proceed to complete heart block.

block.

Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac disturbances. Digoxin may also induce other changes in the ECG (e.g. PR prolongation, ST depression), which represent digoxin effect and may or may not be associated with digitalis toxicity.

Gastrointestinal—Anorexia, nausea, vomiting and less commonly diarrhea are common early symptoms of overdosage. However, uncontrolled heart failure may also produce such symptoms. Digitalis toxicity very rarely may cause abdominal pain and hemorrhagic necrosis of the intestines.

CNS—Visual disturbances (blurred or yellow vision), headache, weakness, apathy and psychosis can occur.

apathy and psychosis can occur.

Other—Gynecomastia is occasion omastia is occasionally observed.

angle Park, NC 2/109

Other—Gynecomastia is occasionally observed.

Infants and Children: Toxicity differs from the adult in a number of respects.

Anorexia, nausea, vomiting, diarrhea and CNS disturbances may be present but are rare as initial symptoms in infants. Cardiac arrhythmias are more reliable signs of toxicity. Digoxin in children may produce any arrhythmia. Yentricular tachyarrhythmias, such as atrial tachycardia with or without block, and junctional (nodal) tachycardia. Yentricular arrhythmias are less common. Sinus bradycardia may also be a sign of impending digoxin intoxication, especially in infants, even in the absence of first degree heart block. Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should initially be assumed to be a consequence of digoxin intoxication.

TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE:

that develops in a child taking digoxin should initially be assumed to be a consequence of digoxin intoxication.

TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE.

Adults: Digoxin should be discontinued until all signs of toxicity are gone. Discontinuation may be all that is necessary if toxic manifestations are not severe and appear only near the expected time for maximum effect of the drug.

Potassium salts are commonly used, particularly if hypokalema is present. Potassium chloride in divided oral doses totaling 3 to 6 grams of the salt (40 to 80 mEq K+) for adults may be given provided renal function is adequate (see below for potassium recommendations in Infants and Children). When correction of the arrhythmia is urgent and the serum potassium concentration is low or normal, potassium should be administered intravenously in 5% dextrose injection. For adults, a total of 40 to 80 mEq (diluted to a concentration of 40 mEq per 500 ml) may be given at a rate not exceeding 20 mEq per hour, or slover limited by pain due to local irritation. Additional amounts may be given if the arrhythmia is uncontrolled and potassium well-tolerated. ECG monitoring should be performed to watch for any evidence of potassium toxicity (e.g. peaking of T waves) and to observe the effect on the arrhythmia. The influsion may be stopped when the desired effect is achieved.

Note: Potassium should not be used and may be dangerous in heart block due to digoxin, unless primarily related to supraventricular tachycardia.

Other agents that have been used for the treatment of digoxin intoxication include lidocaine, procainamide, propranolol and phenytoin, although use of the latter must be considered experimental. In advanced heart block, temporary ventricular pacing may be beneficial. Digoxin immune Fab (Ovine). Digiplind\*, can be used to reverse potentially life-threatening digoxin (or digitoxin) intoxication. Improvement in signs and symptoms of digitalis toxicity usually begins within 2 hour of Digiblind aministration. Each 40 mg vial of

within 12 hour of Digipinic administration. Each au mg wai of Digipinic will neutralize 0.6 mg of digoxin (which is a usual body store of an adequately digitalized 70 kg patient).

Infants and Children: See Adult section for general recommendations for the treatment of arrhythmias produced by overdosage and for cautions regarding the use of potassium.

If a potassium preparation is used to freat toxicity, it may be given orally in divided doses totaling 1 to 1.5 mEq K+ per kilogram (kg) body weight (1 gram of potassium holoride contains 13.4 mEq K+).

When correction of the arrhythmia with potassium is urgent, approximately 0.5 mEg/kg of potassium per hour may be given intravenously, with careful ECG monitoring. The intravenous solution of potassium should be dilute enough to avoid local irritation; however, especially in infants, care must be taken to avoid intravenous full overload.

DOSAGE AND ADMINISTRATION: Recommended dosages are average values that may require considerable modification because of individual sensitivity or associated conditions. Diminished renal function is the most important factor requiring modification of recommended dosser.

In deciding the dose of digoxin, several factors must be considered:

The disease being treated. Atrial arrhythmias may require larger doses than heart failure.

The body weight of the patient. Doses should be calculated based upon lean or ideal body weight.

The patient's renal function, preferably evaluated on the basis of creatinine clearance.

Age is an important factor in infants and children.

Concomitant disease states, drugs or other factors likely to alter the expected clinical response to digoxin (see PRECAUTIONS and Drug Interactions sections).

PRECAUTIONS and Drug Interactions sections).

nsult complete product information before prescribing.

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# Comparison of Outcome of Paramedic-Witnessed Cardiac Arrest in Patients Younger and Older Than 70 Years

Donald D. Tresch, MD, Ranjun K. Thakur, MD, Raymond G. Hoffmann, MD, Tom P. Aufderheide, MD, and Harold L. Brooks, MD

To obtain further information concerning differences in the mechanism of out-of-hospital cardiac arrest between elderly and younger patients, 381 consecutive patients who experienced out-of-hospital cardiac arrest, and whose arrest was witnessed by paramedics, were studied. In 91% of cases the arrest occurred at the time the patient's cardiac rhythm was monitored. Patients were divided into 2 age groups: elderly patients were >70 years (187) and younger patients were <70 years (194). Elderly patients more commonly had a past history of heart failure (25 vs 10%, p < 0.003) and were more commonly taking digoxin (40 vs 20%, p <0.005) and diuretics (35 vs 25%, p <0.004). Before the cardiac arrest, elderly patients were more likely to be complaining of dyspnea (53 vs 40%, p <0.009), whereas younger patients were more likely to complain of chest pain (27 vs 13%, p <0.001). Forty-two percent of younger patients demonstrated ventricular fibrillation as the initial out-of-hospital rhythm associated with the arrest, compared to only 22% of elderly patients (p <0.001). Besides patient age, initial cardiac rhythm varied according to the patient's complaint preceding the arrest. Sixty-eight percent of patients with chest pain demonstrated ventricular fibrillation, whereas only 21% of patients with dyspnea demonstrated ventricular fibrillation. Elderly patients could be as successfully resuscitated as younger patients; however, 24% of younger patients survived, compared to only 10% of elderly patients (p <0.001). Survival was not only dependent on the patient's age, but was dependent on the patient's complaint preceding arrest and the initial cardiac rhythm associated with the arrest. Sixty-five percent of younger patients complaining of chest pain and demonstrating ventricular fibrillation survived. Even in the elderly patients, 58% survived if their complaint was chest pain and if ventricular fibrillation was their initial out-of-hospital rhythm associated with the cardiac arrest.

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ven though sudden cardiac death increases with age, 1-2 the problem of out-of-hospital cardiac arrest in the elderly has not received much attention. In previous studies of out-of-hospital cardiac arrest, 3,4 we found patients >70 years of age could be immediately resuscitated and hospitalized as successfully as patients <70 years of age, although the elderly patients were less likely to survive hospitalization. Another striking difference between the age groups was the higher prevalence in the younger patients of ventricular fibrillation as the initial documented cardiac rhythm associated with the cardiac arrest, whereas in elderly patients the arrest was more commonly associated with a bradyarrhythmia. As expected, patients demonstrating ventricular fibrillation had the best chance of surviving.

This influence of the patient's age on the out-of-hospital cardiac rhythm associated with the cardiac arrest has not been previously reported. It is unknown if the lower prevalence of ventricular fibrillation in the elderly merely reflects a delay of the initiation of resuscitation in this age group, with ventricular fibrillation degenerating into an agonal rhythm, or whether the bradyarrhythmia represents a primary event triggering the cardiac arrest. To obtain further information concerning possible differences in the mechanism of out-of-hospital cardiac arrest between elderly and younger patients, we undertook the present study. In the present study only patients whose arrest occurred in the presence of paramedics were studied: the cardiac arrest occurred after arrival of paramedics and was witnessed by paramedics. In most cases, the patient's cardiac rhythm was monitored before the cardiac arrest.

#### **METHODS**

The Milwaukee County Paramedic Program serves a population of approximately 1,000,000. We have previously described the characteristics of the emergency care system in this community.<sup>5</sup> All paramedic operational (run) data are entered on standard forms and placed in a computer for future retrieval. In addition, all

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TABLE I Prearrest Data							
	Total (381)	Elderly (n = 187)	Younger (n = 194)	p Value*			
Cardiac history (%)							
Heart failure	64 (17)	45 (24)	19 (10)	< 0.003			
Digitalis	113 (30)	74 (40)	35 (18)	< 0.005			
Diuretics	150 (39)	92 (49)	39 (20)	< 0.004			
Myocardial infarction	75 (20)	40 (21)	58 (30)	NS			
Complaints preceding arre	est (%)						
Dyspnea	177 (46)	100 (53)	77 (40)	< 0.009			
Chest pain	77 (20)	24 (13)	53 (27)	< 0.001			
Chest pain and dyspnea	28 (7)	13 (7)	15 (7)	NS			
Loss of consciousness	35 (9)	18 (10)	17 (9)	NS			
Other symptoms	64 (17)	32 (17)	32 (16)	NS			

TABLE II Classification Age Groups	n of Out-of	f-Hospital (	Cardiac Ar	rest by	
	Total (n = 381)	Elderly (n = 187)	Younger (n = 194)	p Value*	
Ventricular fibrillation (%)	123 (32)	42 (22)	81 (42)	<0.001	
Electromechanical dissociation (%)	156 (41)	89 (48)	67 (34)	<0.013	
Asystole (%)	102 (27)	56 (30)	46 (24)	NS	

original records and rhythm strips are kept on file for verification of data.

During a 5-year period (1980 to 1985) consecutive patients ≥30 years of age who sustained out-of-hospital cardiac arrest and whose cardiac arrest was witnessed by paramedics were identified. Initially, 403 patients were identified. Due to incomplete data or inability to accurately interpret electrocardiographic rhythm strips due to faulty recordings, 22 patients were eliminated.

The 381 remaining patients were divided into 2 age groups: elderly patients were >70 years (187) and younger patients were <70 years (194). Paramedic run data were reviewed on each patient and each patient's initial out-of-hospital rhythm strip and the rhythm strip associated with the cardiac arrest were analyzed by us. According to the rhythm strips, each patient's cardiac arrest was classified by the paramedics as being related to ventricular fibrillation, asystole or electromechanical dissociation. As there were only 6 arrests associated with ventricular tachycardia, ventricular fibrillation and ventricular tachycardia were considered as 1 rhythm when classifying the cardiac arrests. As designated in our previous studies, electromechanical dissociation was classified as an electrical complex without a palpable pulse; excluded from the definition were ventricular fibrillation and ventricular tachycardia. Rhythm strips of patients whose arrest was classified by the paramedics as being related to electromechanical dissociation were further analyzed, and the specific rhythm at the time of the electromechanical dissociation was determined.

Patients' complaints before their cardiac arrest were determined, as was each patient's past cardiac history, including cardiac medication. A resuscitation was considered successful if the patient was resuscitated out-of-

TABLE III Relation of Patient's Complaint and Cardiac Arrest Rhythm

	Out-of-Ho Initial Car			
	VF	EMD	Asystole	p Value
Chest pain (n = 77) (%)	52 (68)	19 (25)	6 (8)	<0.0001
Dyspnea (n = 177) (%)	38 (21)	80 (45)	59 (33)	< 0.0005
Chest pain and dyspnea (n = 28) (%)	5 (18)	12 (43)	11 (39)	NS
Loss of consciousness (n = 35) (%)	7 (20)	10 (29)	18 (51)	NS
Other $(n = 64)$ (%)	19 (30)	28 (44)	17 (27)	NS

hospital and admitted to the hospital. Survival was defined as discharge of the patient alive from the hospital.

Data were statistically analyzed by the chi-square or Student t test, as applicable. Multivariate regression analysis was used to determine influence of rhythm, complaints and age of survival.

#### RESULTS

Demographics: The mean age of the elderly patients was  $79 \pm 7$  years (range 71 to 99). The mean age of the younger patients was  $59 \pm 9$  years (range 31 to 69). Seventy-seven patients were >80 years of age and 28 patients were <50 years of age. Ninety-seven (52%) of the elderly group were women, compared to 70 (36%) of the younger group (p < 0.001).

Cardiac history: A significant difference in cardiac history and use of cardiac drugs was noted between the 2 age groups (Table I). Elderly patients more commonly had a past history of heart failure and were more commonly taking digitalis and diuretics. No difference in prevalence of prior myocardial infarction was noted between the age groups.

Symptoms preceding cardiac arrest: Paramedics were usually called because of patients' complaints of dyspnea or chest pain (Table I). Seven percent of patients complained of both chest pain and dyspnea and 17% had other complaints, such as gastrointestinal distress, generalized weakness, dizziness or acute confusion. Nine percent of the patients were unconscious at the time of the arrival of the paramedic unit, and remained unconscious before the cardiac arrest.

Symptoms varied according to the patient's age (Table I). Younger patients, compared to elderly patients, were more likely to be complaining of chest pain before their cardiac arrest, whereas elderly patients more commonly complained of dyspnea. Of the total of 77 patients with chest pain, 69% were younger patients, whereas 56% of the 177 patients with dyspnea were elderly patients.

Documented cardiac rhythm preceding cardiac arrest: In 349 of the 381 patients a cardiac rhythm was documented before the patient's cardiac arrest. The most common rhythm seen was sinus with 160 (46%) patients demonstrating normal sinus, 29 (8%) sinus tachycardia and 22 (6%) sinus bradycardia. Junctional rhythms and atrial fibrillation were also common before the arrest with 40 (11%) patients demonstrating a junctional rhythm and 27 (8%) patients atrial fibrillation. Six (2%) patients had an atrial tachycardia. In 25 (7%) of the patients a slow idioventricular rhythm was documented and ventricular tachycardia was present in 27 (8%) of the patients. Ten (3%) patients demonstrated second or third degree heart block before the arrest. Three (1%) patients demonstrated an electronically paced rhythm.

Initial documented cardiac rhythm associated with cardiac arrest: Of the 381 patients, 123 (32%) demonstrated ventricular fibrillation as the initial documented rhythm associated with their cardiac arrest and 102 (27%) demonstrated asystole. In 156 (41%) patients the cardiac arrest was classified as being related to electromechanical dissociation. In the 150 patients whose rhythm could be determined at the time of the electromechanical dissociation 119 (79%) demonstrated an idioventricular or slow junctional rhythm; 18 (12%) had a sinus rhythm or atrial fibrillation; 10 (7%) had second- or third-degree heart block; and 3 (4%) had an electronically paced rhythm.

Of the 123 patients who demonstrated ventricular fibrillation at the time of their arrest, 116 had a cardiac rhythm monitored before the arrest. In 66 (57%) the rhythm before the arrest was sinus; 24 (21%) had ventricular tachycardia; 12 (10%) had atrial fibrillation; and 9 (8%) had a junctional rhythm. In the remaining 5 (4%) patients with ventricular fibrillation at the time of their arrest, the rhythm before the arrest was idioventricular (3) or second-degree heart block (2).

A significant difference in the prevalence of the initial documented cardiac rhythm at the time of the patient's cardiac arrest was noted between the age groups (Table II). Younger patients more commonly demonstrated ventricular fibrillation at the time of the arrest; in elderly patients the arrest was more commonly classified as being related to electromechanical dissociation and in the majority of patients with electromechanical dissociation the rhythm was a bradyarrhythmia.

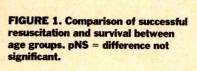
The initial cardiac rhythm associated with the cardiac arrest varied not only according to the patient's age, but was also dependent on the patient's complaint before the arrest (Table III). The majority of patients complaining of chest pain demonstrated ventricular fibrillation while patients complaining of dyspnea more commonly demonstrated asystole, or the arrest was classified as being related to electromechanical dissociation.

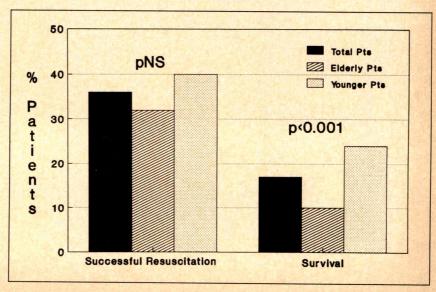
Survival: Of the total 381 patients, 36% were successfully resuscitated and hospitalized, and 17% survived (Figure 1). There was no significant difference in success of immediate resuscitation and hospitalization between the age groups; however, 24% of younger patients survived compared to only 10% of elderly patients (p <0.001). Not only was survival dependent on the patient's age, but the initial cardiac rhythm associated with the cardiac arrest was a significant determinant of survival (Figure 2). Approximately 40% of patients who demonstrated ventricular fibrillation survived compared to only 7% of patients who demonstrated other rhythms. Symptoms also influenced survival (Figure 3). Patients complaining of chest pain before their arrest had the best chance of survival, with 48% surviving, whereas only 7% of patients with dyspnea survived. In the 40 younger patients complaining of chest pain before the arrest and demonstrating ventricular fibrillation at the time of the arrest, 26 (65%) survived. Even in the 12 elderly patients whose complaint was chest pain and whose cardiac rhythm was ventricular fibrillation, 7 (58%) survived.

Using multivariate logistic analyses we found that the patient's age, initial out-of-hospital rhythm and complaint all possessed independent and significant relation to survival. However, the patient's out-of-hospital rhythm and the patient's complaint were better predictors of survival than the patient's age (p <0.0001, p <0.0001, p <0.0005, respectively).

#### DISCUSSION

The findings of the present study corroborate and extend the findings of our previous studies<sup>3,4</sup> comparing





elderly and younger victims of out-of-hospital cardiac arrest. However, it should be stressed that the patient population of the present study is significantly different from our previous studies. The present study included only victims of out-of-hospital cardiac arrest whose arrest was witnessed by paramedics, and in most of cases the patient's cardiac rhythm was monitored at the time of the arrest. Our previous studies included all patients who received resuscitation by paramedics regardless of whether the arrest was witnessed.

The present study, as in our previous studies, demonstrated that elderly patients can be initially resuscitated and hospitalized as successfully as younger patients; however, elderly patients are less likely to survive hospitalization. Initial documented out-of-hospital rhythms associated with the cardiac arrest were different between the age groups, with younger patients more commonly demonstrating ventricular fibrillation, whereas in the elderly patients the arrest was more commonly associated with a bradyarrhythmia. A difference in patients' complaints preceding the arrest was also noted between the 2 age groups; chest pain was more common in younger patients; dyspnea was more common in the elderly patients. The patient's complaint was noted to correlate with the initial documented rhythm associated with the cardiac arrest. In patients complaining of chest pain, ventricular fibrillation was the most common initial documented rhythm associated with the arrest, while in patients with dyspnea the arrest was more commonly associated with bradyarrhythmias.

Survival of the patients was dependent on age, initial cardiac rhythm associated with the arrest and the complaint preceding the arrest. Even though all 3 determinants possessed independent and significant relation to survival, the initial out-of-hospital rhythm and the patient's complaint were better predictors of survival than the patient's age.

The explanation for the differences between the 2 age groups is unclear. It is possible that a difference in the etiology of the cardiac arrest may partially explain the different findings between the age groups. As in previous studies comparing elderly and younger patients with life-threatening ventricular tachyarrhythmias, including cardiac arrest, 4,6 the elderly patients in our pres-

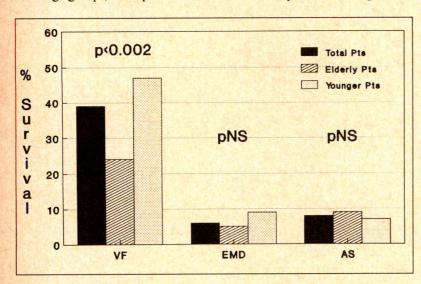


FIGURE 2. Comparison of survival with cardiac rhythms and age groups. AS asystole; EMD = electromechanical disso ciation; VF = ventricular fibrillation. Other abbreviation as in Figure 1.

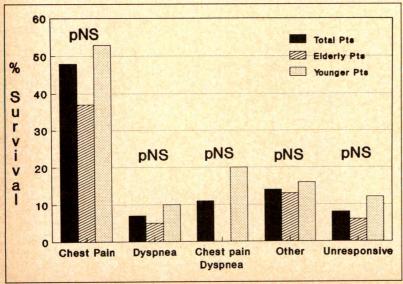


FIGURE 3. Comparison of survival with complaints and age groups. Abbreviation as in Figure 1.

ent study more commonly had a past history of heart failure, and were more commonly taking digoxin and diuretics. Thus, we might assume that the cardiac arrest in some of the elderly patients was precipitated by heart failure, or it is possible that pulmonary disease, which is so common in elderly patients, was the precipitating event. Such an explanation would be compatible with the elderly patient's complaint of dyspnea before the arrest, and may explain the high prevalence of bradvarrhythmias in this age group. In contrast, the increased prevalence of chest pain in the younger patients may reflect that their cardiac arrest more commonly was related to an acute myocardial ischemic event with resultant ventricular fibrillation. Such a difference in the mechanism of the cardiac arrest may even partially explain the difference in the survival of the 2 age groups. Other investigators have recently reported on the role of bradyarrhythmias as a cause of sudden cardiac death. Luu et al7 reported that bradyarrhythmias were frequently the initial rhythm documented at the time of cardiac arrest in patients with chronic heart failure and Luceri et al<sup>8</sup> found bradyasystole to be more common than ventricular fibrillation in patients dying with automatic internal cardioverter defibrillators. In the study of Luceri et al, the mean left ventricular ejection fraction of the patients was 23% and the deaths were due primarily to poor left ventricular dysfunction. Myerburg et al9,10 and Iseri et al11 have also stressed the significance of bradyarrhythmias in producing sudden cardiac arrest, and as in our study, they found survival to be very poor in patients whose arrest was related to a bradyarrhythmia.

Certain findings of our study are at variance with findings of some previous studies of out-of-hospital sudden cardiac arrest. In most studies of out-of-hospital cardiac arrest, 9,12 ventricular fibrillation has been the most prevalent initial documented rhythm associated with the arrest, and chest pain has been the most common symptom preceding the arrest. 13 The high prevalence of bradyarrhythmias and the common complaint of dyspnea in our study may be partially explained by

the design of our study and the patient population. Our patient population comprises a small subset of the total patients sustaining out-of-hospital cardiac arrest in that we only studied patients whose arrest was witnessed by paramedics. Some of the deaths of our patients may not even have been considered sudden by some authorities, as the arrests in certain patients most likely were preceded by symptoms for longer than 1 hour. Nevertheless, even though the design of the study may partially explain the increase in bradyarrhythmias associated with the cardiac arrest and may be responsible for the high prevalence of dyspnea as the preceding complaint, it does not explain the difference in cardiac rhythms and complaints between the age groups.

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# Changes in Cardiac Output Determined by Continuous-Wave Doppler Echocardiography During Propafenone or Mexiletine Drug Testing

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Antiarrhythmic drugs may induce congestive heart failure in patients with malignant ventricular arrhythmias and depressed left ventricular (LV) function. Whether Doppler echocardiography can detect drug-induced depression in LV function was assessed. Continuous-wave Doppler measurements of ascending aortic blood flow velocity were obtained in 16 patients while not receiving antiarrhythmic drugs on 2 consecutive days to assess day-to-day variability, as well as while receiving maximally tolerated oral doses of mexiletine (11 patients) and propafenone (9 patients). While receiving propafenone, a drug with moderate negative inotropic activity, peak flow velocity declined by 9  $\pm$  8% (p <0.05), the flow velocity integral (termed stroke distance, representing stroke volume) declined by 8  $\pm$  11% (p <0.10), the rate-corrected stroke distance declined by  $9 \pm 8\%$  (p <0.02) and the minute distance, representing cardiac output, declined by  $10 \pm 12\%$  (p <0.05). In contrast, while receiving mexiletine, a drug with minimal negative inotropic activity, none of these parameters changed significantly. Five of 9 patients (56%) treated with propafenone showed a decline in rate-corrected stroke distance exceeding the 95% confidence limit of day-to-day variability, which was ± 13 percent. Two of these 5 patients developed clinical signs of congestive heart failure. Continuous-wave Doppler echocardiography can detect antiarrhythmic drug-induced LV dysfunction and may be used to anticipate the development of significant clinically overt congestive heart failure. (Am J Cardiol 1990;65:458-462)

mpairment of left ventricular function (LV) is an important side effect common to many antiarrhythmic drugs. Patients with malignant ventricular arrhythmias usually have LV dysfunction and can ill afford further myocardial depression by drugs prescribed to improve survival. Since invasive hemodynamic monitoring is not routinely used during antiarrhythmic drug testing, recognition of this side effect depends on frequent clinical examinations and the development of congestive heart failure. However, the physical examination is an insensitive tool for the detection of drug-induced LV dysfunction. Doppler echocardiography is a diagnostic technique that allows noninvasive determination of LV function. The Doppler-determined peak flow velocity and the product of flow velocity integral and cross-sectional area of the aortic anulus have been shown to correlate well with invasive measurements of LV function.<sup>2,3</sup> Doppler echocardiography has been used to assess changes in LV stroke volume and cardiac output after the intravenous administration of drugs.4-6 However, it is not known whether changes in LV function occurring over several days of treatment with antiarrhythmic agents can be detected by this method. To answer this question we compared changes in Doppler measurements of LV function before and after administration of mexiletine, an antiarrhythmic drug with minimal negative inotropic properties,7 and propafenone, which has been shown to depress myocardial contractili-

#### METHODS

Study population: We evaluated 25 patients, of whom 21 were men and 4 were women. The mean age was 60 years (range 27 to 76). All patients were admitted to the hospital for the evaluation and treatment of ventricular arrhythmia. The indications for therapy were sustained ventricular tachycardia in 15 (60%), nonsustained ventricular tachycardia in 8 (32%) and symptomatic ventricular ectopic activity in 2 (8%). Twenty patients had heart disease: 14 patients had coronary artery disease; 6 patients had idiopathic cardiomyopathy. Five patients were free of structural heart disease. The mean LV ejection fraction, determined by radionuclide ventriculography, was 36% (range 8 to 67). Ten patients (40%) had a history of congestive heart failure.

**Study protocol:** The protocol for evaluating antiarrhythmic drug efficacy has been previously described. The phase 0 period is an antiarrhythmic drug-free evaluation consisting of 48 hours of ambulatory monitoring,

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TABLE I Percent Change in Doppler Parameters of Left Ventricular Function Between Day 1 and 2 of Phase 0 Testing

	PFV	ET	SD	SDc	MD
bility (%)	5 ± 3	5 ± 4	8±5	5±5	9±5
relation coefficient	0.94	0.90	0.93	0.95	0.87
% confidence interval	±11	± 13	±19	±13	± 23

Variability =  $(day 1 - day 2)/mean (day 1 + day 2) \times 100$ . ET = ejection time; ETc = rate-corrected ejection time; MD = minute distance; PFV = peak flow velocity; SD = stroke distance; SDc = rate-corrected stroke distance.

TABLE II Changes in Heart Rate, Peak Flow Velocity, Ejection Time, Stroke Distance, Rate-Corrected Stroke Distance and Minute Distance

	No therapy (n = 16)			Mexiletine (n = 11)			Propafenone (n = 9)		
	Day 1	Day 2	Δ%	Before	After	Δ%	Before	After	Δ%
HR (beats/min)	72 ± 14	72 ± 12	0 ± 15	74 ± 15	73 ± 13	0 ± 13	73 ± 15	71 ± 15	$-1 \pm 18$
PFV (cm/s)	$100 \pm 21$	101 ± 19	+1 ± 6	106 ± 22	$106 \pm 21$	0 ± 11	111 ± 32	$101 \pm 26$	-9±8*
ET (ms)	$256 \pm 35$	$254 \pm 34$	0±6	249 ± 39	$250 \pm 39$	+1 ± 8	243 ± 35	242 ± 33	0±6
SD (cm)	$15.2 \pm 4.4$	$15.2 \pm 4.3$	$+1 \pm 10$	$15.6 \pm 4.7$	$15.6 \pm 4.5$	+1 ± 15	$15.9 \pm 5.4$	$14.4 \pm 4.7$	-8 ± 11
SDc (cm)	$22.1 \pm 5.2$	$22.1 \pm 4.9$	0±7	$23.0 \pm 5.0$	$22.9 \pm 4.9$	0 ± 12	$23.6 \pm 7.2$	$21.4 \pm 6.6$	-9 ± 8†
MD (cm)	$1,058 \pm 247$	$1,059 \pm 252$	0 ± 12	$1,099 \pm 199$	$1.090 \pm 203$	0 ± 12	$1.123 \pm 365$	$1.023 \pm 379$	$-10 \pm 12$

HR = heart rate. Other abbreviations as in Table I.

a treadmill exercise tolerance test and a radionuclide ventriculogram. A standard 2-dimensional Doppler echocardiogram was performed on all 25 patients during the phase 0 evaluation. In 16 patients, continuous-wave Doppler measurements of ascending aortic blood flow velocity were obtained on days 1 and 2 of the antiarrhythmic drug-free evaluations to determine the temporal variability.

Phase 2 testing is a short-term antiarrhythmic drug trial. Seventeen patients underwent a phase 2 evaluation of either oral mexiletine (11 trials) or oral propafenone (9 trials). For mexiletine the starting dose was 600 mg/day and the maximum daily dose was 900 mg. The starting dose of propafenone was 450 mg/day and the maximum daily dose was 900 mg. Once a steady-state drug level was achieved (5 half-lives), ambulatory monitoring, exercise tolerance testing and echo Doppler measurements of LV function were repeated.

Data acquisition: Blood pressures were recorded by sphygmomanometry in all patients at rest. LV ejection fraction was determined by 2-dimensional echocardiography using the 5/6 area-length method. 10 Doppler studies of blood flow velocities were recorded during quiet respiration with the patients in the left lateral position using a freestanding, nonimaging 1.9-MHz continuous-wave transducer connected to a Hewlett Packard 77020 ultrasonoscope. Ascending aortic Doppler blood flow velocity spectra were recorded on a strip chart at a paper speed of 50 mm/s using the audible signal to obtain the maximal amplitude. Doppler velocity spectra were recorded from the apical transducer position in all but 3 patients, in whom the maximal flow velocities were acquired from a suprasternal position. In addition, care was taken to record flow velocity profiles with well-defined spectral envelopes and the high-frequency signals of aortic valve openings and closures so that the ejection time could be measured.

Doppler measurements and data analysis: Three consecutive high quality flow velocity spectral envelopes

with maximum amplitudes were selected in each patient. Measurements were made of the peak flow velocities (PFV) and the ejection times (ET), which was taken from the leading edge of the high frequency opening sound to the leading edge of the closing sound of the aortic valve cusps. The 3 observations were then averaged. The flow velocity integral, or stroke distance (SD) (according to Haites et al11), was calculated with the use of the formula: SD =  $(PFV \times ET)/2 \times 1.14 + 0.3$ . The calculated SD has been shown to correlate closely with the SD obtained by planimetry. 4 Heart rate (HR) was measured from the RR interval of the simultaneously recorded electrocardiogram. Minute distance (MD), which is a measure of cardiac output, was calculated as:  $MD = SD \times HR$ . To adjust for the differences in HR between separate recordings, rate-correction of ejection time was performed according to the formula of Weissler et al.12 The rate-corrected ejection time (ETc) was calculated as: ETc = ET +  $(1.7 \times HR)$ . Rate-corrected stroke distance (SDc) was calculated as:  $SDc = (PFV \times ETc)/2 \times 1.14 + 0.3$ . Since the aortic anulus is nearly constant despite changes in LV function,13 we did not convert the Doppler indexes of SD and MD to their physiologic correlates of stroke volume and cardiac output. All the Doppler recordings were measured by 2 blinded observers. In addition, 1 observer made the measurements twice with an intervening time period of 2 weeks. To determine intra- and interobserver variability, 3 blinded observations of 32 Doppler studies in the 16 patients studied twice during phase 0 were compared. As a measure of variability the difference between 2 observations was calculated and expressed as percent of the mean of the 2 observations. The results of all 3 blinded observations were averaged for each study in an individual patient during both the temporal variability in Doppler measurements study and during the drug therapy study.

Statistical analysis: Values for continuous variables are presented as the mean  $\pm 1$  standard deviation.

Changes in hemodynamic and Doppler measurements were tested by paired t test. Differences between groups were tested by analysis of variance. Linear correlation coefficients were calculated to compare Doppler observations on day 1 and day 2 of phase 0 (temporal variability). A p value <0.05 was considered significant.

#### RESULTS

Variability in Doppler measurements: Intraobserver variability for peak flow velocity was  $1 \pm 2\%$ , for ejection time  $2 \pm 2\%$  and for stroke distance  $2 \pm 2\%$ . Interobserver variability for peak flow velocity was  $2 \pm 2\%$ , for ejection time  $2 \pm 2\%$  and for stroke distance  $3 \pm 3\%$ . Data on the day-to-day variability (percent change) in Doppler parameters are listed in Table I.

Effect of antiarrhythmic therapy: Changes in hemodynamic and Doppler measurements without therapy as well as after antiarrhythmic therapy with mexiletine and propafenone are listed in Table II. Mean heart rate and blood pressure remained unchanged during the temporal variability studies as well as after mexiletine and propafenone. Doppler measurements of LV function were unchanged during temporal variability studies as well as after mexiletine therapy. In contrast, administration of propafenone was associated with a significant decline in peak flow velocity (-9%), rate-corrected stroke distance (-9%) and minute distance (-10%). The decrease in stroke distance (-8%) failed to reach statistical significance (p = 0.09). Ejection time did not change significantly in any of the 3 groups. The decrease in all Doppler-derived measures of LV function while receiving propafenone was significantly greater

than the changes observed during the temporal variability study. Analysis of individual changes in Doppler measurements (Figures 1 and 2) revealed that 5 of 9 patients (56%) receiving propafenone showed a decrease in rate-corrected SD greater than the 95% confidence limit for temporal variability of this parameter (Figure 1C). There were 2 patients in whom propafenone caused clinical congestive heart failure. Both were among the 5 patients with a profound decline in ratecorrected SD. In contrast, a decrease in rate-corrected SD exceeding the 95% confidence limit of temporal variability occurred in only 1 patient receiving mexiletine (p <0.02). This patient did not develop congestive heart failure. A decrease in Doppler parameters while receiving propafenone exceeding the 95% confidence limit for temporal variability occurred less frequently for peak flow velocity (3 patients), SD (3 patients) and MD (1 patient). For each of these parameters, 1 patient with clinical signs of congestive heart failure could not be identified using the criterion of a >95% confidence limit decline in Doppler parameters. LV ejection fraction by 2-dimensional echocardiography was measured during 7 phase 0 evaluations and 12 drug trials. LV ejection fraction was unchanged on day 1 and day 2 while not receiving antiarrhythmic drugs (40 ± 15 and  $39 \pm 11\%$ , respectively, difference not significant). The 95% confidence interval for temporal variability of 2-dimensional echo-derived LV ejection fraction was ±16%. LV ejection fraction was 38 ± 13% before and 31 ± 14% during therapy with propafenone (difference not significant), and  $42 \pm 15\%$  before and  $37 \pm 14\%$ during therapy with mexiletine (difference not signifi-

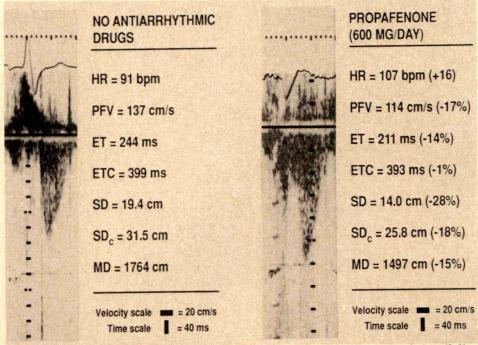


FIGURE 1. A representative recording of the continuous-wave Doppler velocity profile of a patient before (*left*) and after (*right*) administration of propatenone. The decline in the flow velocity integral (stroke distance) is less pronounced after correction for the increase in heart rate (rate-corrected stroke distance): -28% before and -18% after rate correction. ET = ejection time; ETC = rate-corrected ejection time; HR = heart rate; MD = minute distance; PFV = peak flow velocity; SD = stroke distance; SD<sub>c</sub> = rate-corrected stroke distance.

cant). The decline in LV ejection fraction while receiving propafenone was not significantly different from changes during phase 0 or mexiletine drug testing.

#### DISCUSSION

This study demonstrates that oral administration of propafenone, an antiarrhythmic drug with moderate negative inotropic activity, was associated with a significant diminution in the Doppler echocardiographically measured blood flow velocity profile in the ascending aorta. Moreover, a high percentage of patients (56%) receiving propafenone had a decrease in SD, corrected for heart rate, that exceeded the 95% confidence limit for a change in this parameter due to temporal variability alone. Furthermore, 2 of the 5 patients with a significant decrease in Doppler-determined forward flow developed clinical congestive heart failure. In contrast, Doppler measurements of the aortic blood flow velocity profile remained unchanged after administration of mexiletine, a drug without significant negative inotropic activity.

Previous studies using Doppler echocardiography to assess drug-induced changes in LV function have demonstrated that Doppler-determined changes in stroke volume and cardiac output correlate with changes obtained by invasive techniques, such as thermodilution or the Fick method.4-6 However, in these studies, drugs were administered intravenous ly and measurements of LV function obtained within a short period of time, thereby minimizing the effects of temporal variability on Doppler measurements. Our study shows that temporal variability can be reduced to a 95% confidence limit of <15% using a simple heart rate correction of SD, the Doppler correlate of stroke volume. This approach enabled us to identify the majority of patients who sustained small but significant declines in LV function.

Continuous-wave Doppler measures of LV function offer advantages over other noninvasive methods. Two-dimensional echocardiography is frought with a considerable interobserver as well as temporal variability and may therefore be too insensitive to detect small drug-

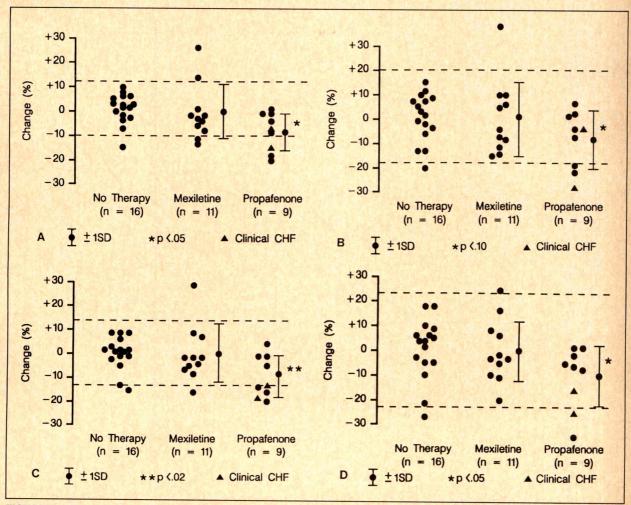


FIGURE 2. Individual data for percent changes in Doppler parameters with no therapy, indicating temporal variability (*left*), with mexiletine (*middle*) and with propafenone (*right*). The *interrupted lines* indicate the 95% confidence limits for temporal variability. A, data for peak flow velocity. B, data for stroke distance (SD). C, data for rate-corrected stroke distance. D, data for minute distance. Note that the incidence of a decline in Doppler parameters with propafenone exceeding the 95% confidence limit of temporal variability was highest for rate-corrected stroke distance (SDc) (5 patients) and lowest for minute distance (1 patient). CHF = congestive heart failure.

induced changes in LV ejection fraction. Although radionuclide ventriculography is less affected by variability, 14 Brodsky et al 15 were unable to detect changes in LV ejection fraction determined by radionuclide ventriculography in patients with congestive heart failure treated with propafenone, despite the known negative inotropic effects of propafenone in these patients.

Our results show that Doppler echocardiographic monitoring of forward blood flow during antiarrhythmic drug testing may be an alternative technique for the noninvasive identification of patients in whom the antiarrhythmic therapy has led to a decline in LV function.

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# Electrophysiologic Determinants of Recurrent Atrial Flutter After Successful Termination by Overdrive Pacing

Heinz D. Gössinger, MD, Peter Siostrzonek, MD, Michael Jung, MD, Ludwig Wagner, MD, and Herbert Mösslacher, MD

The potential ability of electrophysiologic abnormalities to predict recurrence of atrial flutter was evaluated. Twenty-five patients with chronic atrial flutter resistant to combined digitalis and quinidine therapy were studied electrophysiologically after restoration of sinus rhythm by overdrive pacing or by eventual direct current cardioversion. Recurrence of atrial flutter was observed in 12 patients during a mean follow-up period of 17 months (range 3 to 50). Electrophysiologic testing included programmed high right atrial stimulation at a paced drive cycle length of 600 ms and incremental pacing up to 200-ms paced intervals. When coupling intervals of 90% of the drive cycle length were compared to coupling intervals of 48% of the drive cycle length, the increase in S1A1 interval, defined as the interval between the stimulus artifact and the atrial activation near the atrioventricular junction, was greater in patients with subsequent recurrence of atrial flutter (47  $\pm$  11 vs 21  $\pm$  18 ms). Stepwise logistic regression analysis identified the S1A1 increase to be the sole independent predictor of recurrence (p = 0.0082) while previous episodes of atrial flutter or the presence of organic heart disease were identified as dependent variables. Reclassification showed a 91% sensitivity and a 92% specificity. Correct classification was achieved in 92% of patients. The initiation of atrial dysrhythmia had no predictive value. The assessment of the S<sub>1</sub>A<sub>1</sub> interval by programmed atrial stimulation appears helpful in delineating the patient risk of recurrent atrial flutter after termination by overdrive pacing.

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trial flutter has been shown to be associated with marked intraatrial and interatrial conduction delay during sinus rhythm<sup>1,2</sup> or with a heterogeneity in effective atrial refractory periods<sup>3</sup> when compared to normal subjects. We studied whether the response to atrial stimulation subsequent to successful atrial flutter termination by overdrive pacing could be helpful in delineating the patient risk of recurrence of atrial flutter.

## **METHODS**

Patients: Between May 1985 and March 1989, 25 consecutive patients with chronic atrial flutter resistant to digitalis and quinidine were studied prospectively. Atrial flutter with negative flutter waves in leads II, III and aVF had been present for a mean of 4.5 weeks (range 1 to 12). The population age was  $63 \pm 9$  years. There were 20 men and 5 women. Seventeen patients (68%) had organic heart disease. Coronary heart disease was present in 6 patients, with remote myocardial infarction in 4 of them. Four patients had dilated cardiomyopathy. Valve disease was present in 3 patients. Four patients had cor pulmonale. Left ventricular ejection fraction was assessed by M-mode echocardiography or by ventriculography; the mean was  $54 \pm 13\%$ . Lung scintigraphy was consistent with recent pulmonary embolism in 6 patients. In 6 patients earlier episodes of atrial flutter were documented. There was no evidence of prior atrial fibrillation in any patient.

Termination of atrial flutter: The invasive study was aimed at the termination of atrial flutter by overdrive pacing. All patients gave informed consent. The patients were studied in the nonsedated, postabsorptive state. Antiarrhythmic drug therapy had been discontinued 5 half-lives before the study. Twenty-three patients were receiving digitalis for appropriate control of heart rate.

From a right femoral vein approach 3 multipolar electrode catheters were inserted into the high right atrium, in the vicinity of the atrioventricular junction allowing registration of His bundle deflection and into the right ventricular apex under fluoroscopy. Intracardiac recordings were obtained by the use of a mingograph (Siemens-Elema) at a paper speed of 100 mm/s. Simultaneously, the surface electrocardiogram was recorded from leads II, aVF and V<sub>1</sub>. The stimuli were of 20-mA intensity and of 2-ms duration. Overdrive pacing at the high right atrial site commenced at paced intervals 10 ms longer than the flutter wavelength. The duration of

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**TABLE I** Characteristics of Patients With or Without Recurrence of Atrial Flutter After Termination by Overdrive Pacing

	Follow-Up		
	AF	No AF	
	(n = 12)	(n = 13)	p Value
Demographics			
Age (yrs)	$64 \pm 9$	$63 \pm 10$	NS
M/F	3/9	2/11	NS
AF duration (weeks)	$5\pm4$	3±3	NS
Prior episodes of AF (n)	5	1	0.03
Heart disease (n)	11	6	0.058
LVEF (%)	$52 \pm 14$	$54 \pm 13$	NS
Prior pulmonary embolism	3	3	NS
AF cycle length (ms)	$250 \pm 34$	$225 \pm 27$	NS
Heart rate during AF (beats/min)	$96 \pm 25$	$107 \pm 34$	NS
Digitalis use	12	11	NS
Mode of AF termination			
Overdrive pacing/CV ratio	11/1		NS
Cycle length leading to SR (ms)	$207 \pm 32$	$173 \pm 25$	NS
Electrophysiologic findings after			
restoration of SR			
P-wave duration (ms)	$121 \pm 14$	$125 \pm 16$	NS
PA interval (ms)	$47 \pm 14$		NS
AH interval (ms)	$112 \pm 24$		NS
HV interval (ms)	$53 \pm 26$		NS
ERP-A (ms)	$237 \pm 42$		NS
CSNRTmax >550 ms	5	4	NS
S <sub>1</sub> A <sub>1</sub> at coupling interval of	$58 \pm 27$	$57 \pm 22$	NS
90% of drive cycle length (ms)			
S <sub>1</sub> A <sub>1</sub> at coupling interval of	$105 \pm 28$	$78 \pm 27$	0.02
48% of drive cycle length (ms)			
S <sub>1</sub> A <sub>1</sub> increase (ms)	$47 \pm 11$	$21 \pm 18$	0.0003
Initiation of single atrial beats	4	2	NS
Initiation of AF	0	3	NS

AF = atrial flutter; AH = atrioventricular nodal conduction time; CSNRTmax = maximal corrected sinus node recovery time; CV = electrical cardioversion; ERP-A = effective atrial refractory period; HV = infranodal conduction time; LVEF = left ventricular ejection fraction; NS = not significant; S<sub>1</sub>A<sub>1</sub> = interval between high right atrial extrastimulus artifact and consecutive low right atrial activation; SR = sinus rhythm.

pacing was 20 to 30 seconds for every paced interval. There was a stepwise decrease of 10 ms after every failed pacing attempt. If pacing did not succeed until a paced interval of 120 ms, the catheter was moved to a different pacing site for repetition of the entire pacing procedure.

If induced atrial fibrillation did not revert spontaneously to sinus rhythm within 30 minutes, direct current cardioversion was performed under short-term general anesthesia using etomidate, 0.15 mg/kg intravenously. A time interval of 1 hour was selected between the restoration of sinus rhythm and the subsequent electrophysiologic study, which provided safe return to electrophysiologic baseline conditions.<sup>4</sup>

Electrophysiologic testing: Atrial stimulation was performed with the pacing electrode positioned at the high right atrium. The stimuli had a 2-ms duration at twice diastolic threshold. Single extrastimuli were coupled to the paced drive cycle length of 600 ms, with the coupling intervals stepwise shortening by 10 ms from 580 ms until the effective refractory period was reached. The corrected sinus node recovery time was determined as described earlier. Incremental pacing was performed from 600-ms paced intervals up to paced

intervals of 200 ms. The paced interval decreased stepwise by 10 ms after every paced beat.

Conduction intervals: P-wave duration was determined by measuring the onset to termination of the longest P wave on the surface electrocardiographic leads. PA intervals were determined as the interval between the earliest onset of the P wave on the surface leads to the earliest atrial activation near the atrioventricular junction. The atrioventricular nodal and infranodal conduction times were determined as reported earlier.<sup>2</sup> The S<sub>1</sub>A<sub>1</sub> intervals were determined for coupling intervals at 90% of the basic drive cycle length and for coupling intervals of 48% of the drive cycle length. The S<sub>1</sub>A<sub>1</sub> interval was defined as the interval between the stimulus artifact and the earliest atrial activation recorded from the vicinity of the atrioventricular junction. The flutter cycle length was defined as the interval between 2 consecutive flutter waves recorded from the high right atrial site. Electrophysiologic variables were averaged out of 5 individual measurements where appropriate.

Treatment and follow-up: No antiarrhythmic medication was allowed until recurrence of atrial flutter. Patients with suspected pulmonary embolism received anticoagulant treatment. The patients were followed up clinically at 6-month intervals. In 6 patients information was obtained by telephone contact with the patients, the physician in charge and family members. After recurrence of atrial flutter the patients were eliminated from follow-up.

Statistical analysis: The numerical results are expressed as mean ± standard deviation. Chi-square tests were used to compare discrete variables for different patient groups. A 1-way analysis of variance was applied for comparison of continuous variables. A stepwise multiple logistic-regression model<sup>6</sup> was applied to variables (increase in S<sub>1</sub>A<sub>1</sub> interval during programmed atrial stimulation, prior flutter episodes, presence of organic heart disease) that best classified recurrence of flutter. The final logistic regression model was applied to the study population for assessment of sensitivity, specificity and predictive accuracy. Estimates of recurrence of atrial flutter were made from the follow-up data by the use of a Kaplan-Meier analysis. Statistical differences for the recurrence curves were determined by the tests of Mantel-Cox and Breslow. Significance was assumed with a p value <0.05.

# RESULTS

Mode of termination: Successful conversion to sinus rhythm was achieved in all 25 patients either by over-drive pacing (20) or by eventual direct current cardioversion in case of persistence of induced atrial fibrillation (5).

Follow-up data: The mean duration of follow-up was 17 months (range 3 to 50). Recurrence of atrial flutter occurred in 12 patients. Thirteen patients maintained sinus rhythm. The time interval from electrophysiologic evaluation until completion of follow-up was similar for both groups. There were 2 patients in either group receiving antiarrhythmic treatment not based on the occurrence of atrial dysrhythmia. Five patients died for

reasons unrelated to atrial flutter. Nine of 10 patients with prolonged sinus node recovery time required pacemaker implantation during the follow-up period although digitalis medication was discontinued when symptomatic bradycardia occurred.

Comparison of patients with maintenance of sinus rhythm and patients with recurrent atrial flutter: Table I lists demographics, the termination modes of atrial flutter and electrophysiologic findings after restoration of sinus rhythm for both patient groups with recurrence of atrial flutter and patients with maintenance of sinus rhythm. The significant difference in S<sub>1</sub>A<sub>1</sub> increase reflected the increase in right atrial conduction time as the interval from the high right atrial activation to the subsequent low septal deflection. With shortening of the coupling interval the increase in intraatrial conduction time was 39 ± 12 ms for patients with later relapse of atrial flutter and 18 ± 18 ms for patients without recurrent atrial flutter (p = 0.03). The local delay between the stimulus artifact and the high right atrial activation was similar in both groups, irrespective of the applied coupling interval.

The increase in the  $S_1A_1$  interval did not significantly differ among 6 patients with a history of prior episodes of atrial flutter (52  $\pm$  8 ms) and 7 patients without prior events of atrial flutter but subsequent recurrence of atrial flutter (42  $\pm$  11 ms). Induced atrial flutter reverted to sinus rhythm spontaneously in 2 patients and was terminated by rapid pacing in 1 patient.

**Statistical prediction model:** By a multivariate stepwise logistic regression procedure the increase in the  $S_1A_1$  interval was identified to be the sole but powerful predictor of recurrent atrial flutter (p = 0.0082). The presence of organic heart disease and a history of prior episodes were eliminated as dependent variables. The reclassification matrix revealed a 91% sensitivity and a 92% specificity. Ninety-two percent of patients were reclassified correctly, indicating an excellent fit to the model of logistic regression.

**Estimates of recurrence of atrial flutter:** The projected recurrence rate at 2 years was 51% for the entire study population. Since the aforementioned model did

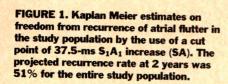
not consider the individual observation time, the median value of the  $S_1A_1$  increase (37.5 ms) was arbitrarily selected as the division point for Kaplan-Meier analysis. The results are shown in Figure 1. At 2 years the projected recurrence rate of atrial flutter was 8% for patients with an  $S_1A_1$  increase  $\leq$ 37.5 ms and 80% in patients with an  $S_1A_1$  increase  $\geq$ 37.5 ms. The estimated recurrence curves were significantly different both by tests of Mantel-Cox (p = 0.0028) and Breslow (p = 0.0047).

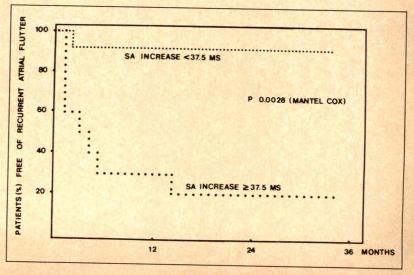
# DISCUSSION

Patients successfully reverted from chronic atrial flutter to regular sinus rhythm have a variable rate of recurrence of atrial flutter. The present study indicates that by programmed atrial pacing subsequent to successful termination by endocavitary overdrive pacing, a greater  $S_1A_1$  delay at shorter coupling intervals allows prediction of recurrence of atrial flutter. Although the predictive value of the  $S_1A_1$  increase awaits prospective validation, the correct reclassification in 92% of patients favors clinical applicability.

Prior reports: Pure atrial flutter differs from atrial fibrillation in many ways, in particular in respect to relapse rate. Earlier information suggested that a left atrial size <45 mm, a left ventricular ejection fraction >45%, the absence of previous flutter episodes and the absence of organic heart disease may identify patients with the ability to maintain sinus rhythm after successful cardioversion of atrial flutter. However, the value of those predictors was hampered by a 60% sensitivity, which mirrors in some way the results of the present regression analysis, indicating that organic heart disease and prior flutter episodes were dependent variables.

Atrial conduction abnormalities: Atrial flutter virtually means reentry within the right atrium while the left atrium acts as an "innocent bystander." Regardless of the atrial size, prolonged PA intervals and prolonged P-wave duration at rest characterize patients with a history of atrial flutter, but lack any predictive value (Table I). Patients with spontaneous flutter or fibrillation have more intraatrial conduction delay at short





coupling intervals of extrastimuli than patients without arrhythmia.3,11,12 The present study indicates that a greater increase in S1A1 intervals at 600-ms paced drive cycle length predicts a higher risk of recurrence of atrial

Patients with prior flutter episodes, who are a priori at higher risk of recurrent atrial flutter by clinical standards,8 had a similar S1A1 increase when compared to patients with subsequent relapse but without a history of previous flutter events. Therefore, it may be speculated that the greater prolongation of S1A1 intervals in patients with subsequent recurrence of atrial flutter reflects the enhanced atrial ability to create significant conduction delay, which could explain the propensity for recurrence of atrial reentry.

Induction of atrial arrhythmia: The induction of atrial flutter had no predictive value in the present study. This finding may be blunted by the failure to induce atrial flutter in the majority of patients, which contrasts to data on the feasibility of reproducing clinical atrial flutter in the electrophysiologic laboratory. 10 This discrepancy is probably due to the applied stimulation protocol, which was designed to be less aggressive to avoid induction of nonclinical atrial fibrillation. In fact, this type of arrhythmia was induced in none of the

Study limitations: In agreement with general clinical practice, 13-15 the present results were obtained with most of the patients receiving digitalis. Digitalis has been reported to prolong intraatrial conduction. 16,17 However, the prevalence of digitalis use was similar in both patients with and without recurrence of atrial flut-

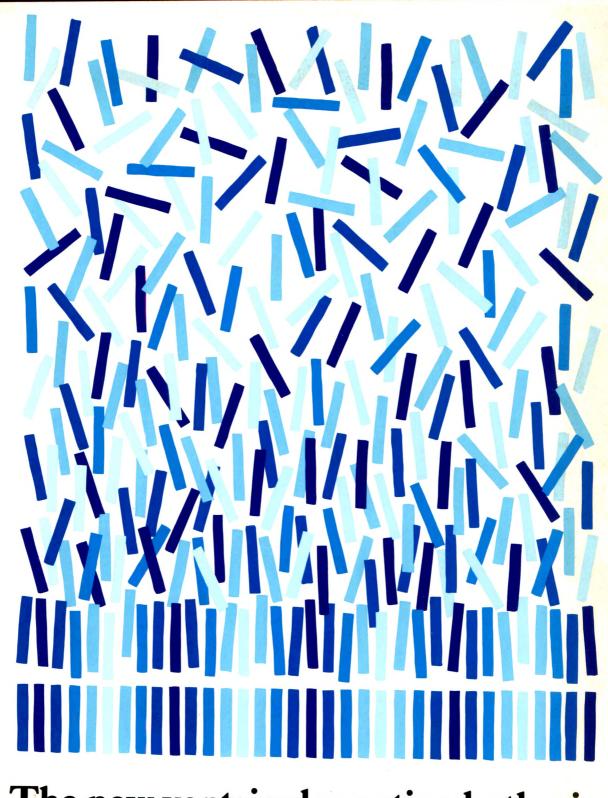
Since interatrial conduction times and effective refractory periods from different atrial sites were not measured, potential effect on the predictive value of the  $S_1A_1$  increase cannot be excluded.

Additionally, the relatively small number of patients may somewhat limit the significance of the present find-

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# Proven in studies on patients with sustained V-Tach:

- 10%²-36%³ of patients achieved complete suppression of inducible VT during invasive electrophysiologic testing. Slowing of the inducible VT rate was seen in a large percentage of patients not completely suppressed.
- In three separate studies,  $39\%^2$  (n = 14/36),  $67\%^4$  (n = 32/48) and  $91\%^5$  (n = 10/11) of patients with VT/VF who were initially discharged on Rythmol achieved long-term therapy success.

# Vaughan Williams Class 1C with beta blocking activity equal to 1/40 that of propranolol\*

\*Patients with bronchospastic disease should, in general, not receive propafenone.

1. Singh BN, et al. *American Heart J* 116 (5): 1542-1551, 1988. 2. Haffajee CI, et al. *Circ*. 80 (4): II-652, 1989. 3. Valero de Pesce EM, et al. *J. Electro* 2 (3): 215-221, 1988. 4. Dugernier TH, et al. *JAAC* 9 (2): 244A, 1987. 5. Budde TH, et al. *Eur Heart J* 8 (S2): 97, 1987.



Safety Profile Based on 2,127 Patients Studied up to 5 Years Cardiac: Discontinuance due to cardiac adverse effects within the first month of study: 3.6% at starting dose (450 mg); 4.9% at high dose (900 mg). Of 2,127 patients in the study, 971 had malignant arrhythmias at baseline.

**Proarrhythmia incidence 4.7%:** In 2,127 patients studied at recommended dosages in U.S. multicenter trials, proarrhythmia was manifested as ventricular tachycardia/fibrillation in 4% of the patients, and as increased PVCs in 0.7%.

Of the patients who had new or worsening VT(4%), 92% had a history of VT and/or VT/VF, 71% had coronary artery disease, and 68% had a prior myocardial infarction. The incidence of proarrhythmia in patients with less serious or benign arrhythmias (a disease state for which the drug is not indicated) which include patients with an increase in frequency of PVCs, was 1.6%. Most proarrhythmic events occurred during the first week of therapy.

**Non-Cardiac:** 1.9% or less discontinuance due to non-cardiac side effects in each of the other body systems at 450 mg/day.

6. Data on file, Knoll Pharmaceuticals



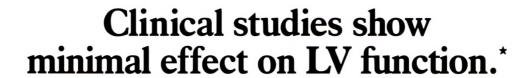
# Minimal Effect on LV Function

with

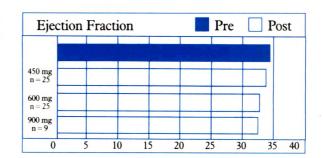
# CHF Incidence 3.7% in 2,127 Patients

Of the 3.7%:

- 80% of patients had pre-existing CHF.
- 85% had CAD.
- 0.2% of patients without a prior history of CHF, attributed CHF to Rythmol.



Study I – In 26 patients with a mean ejection fraction under 35%, no statistically significant decrease in LV ejection fraction was seen as the dose was increased from 450 mg to 900 mg from baseline.



Baker, et al, Practical Card 14: 117, 1988.

Study II – In 12 patients with ejection fractions under 40%, no significant reduction of LV ejection fraction was seen as determined by nuclear ventriculography.

Brodsky, et al, Am Heart J;110:794-799, 1985.

Study III – 42 patients were studied by radioventriculography in control and during propafenone therapy. For the group as a whole, propafenone did not affect LVEF (47% vs 45%, p=NS).

Cueni, L; Podrid, PJ; Jrnl Electrophysiology 1:6, 548-560, 1987.

<sup>\*</sup>Rythmol® exhibits both a beta blocking and a dose related negative inotropic effect. Patients with CHF should be fully compensated before Rythmol therapy is initiated.

	LVEI Control	F (%) Drug
All (37 42)		
All patients (N = 42)	47	45
Responders (N = 21)	46	44
Nonresponders (N = 21)	49	47
<b>LVEF</b> > 50%	60	57
<b>LVEF</b> < 50%	34	33
LVEF < 30%	23	22



# Concomitant Use Experience

With digitalis. Rythmol (propafenone HCl) produces dose related increases in serum digoxin levels. Patients on Rythmol plus digoxin therapy should have plasma levels measured. Digoxin dosage should ordinarily be reduced when Rythmol is started.

With warfarin. In patients receiving Rythmol and warfarin concomitantly, warfarin mean steady-state plasma concentrations increased 39% with corresponding increase in prothrombin times of approximately 25%. It is therefore recommended that prothrombin times be routinely monitored, and the dose of warfarin be adjusted if necessary.

With propranolol. Concomitant administration of Rythmol and propranolol has resulted in substantial increases in propranolol plasma concentration and elimination half-life with no change in propafenone plasma levels from control values. While the therapeutic range for beta blockers is wide, a reduction in dosage may be necessary during concomitant administration with Rythmol.

With calcium channel blockers. Concomitant therapy of Rythmol with diuretics and calcium channel blockers has been reported without evidence of clinically significant adverse reactions.

With cimetidine. In normal patients concomitant administration of Rythmol and cimetidine resulted in a 20% increase in steady-state plasma concentrations of Rythmol with no detectable changes in electrocardiographic parameters beyond that measured on Rythmol alone.



INDICATIONS AND USAGE

RYTHMOL (propafenone HCl) is indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that in the judgement of the physician, are life threatening. Because of the proarrhythmic effects of RYTHMOL, its use should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks. The use of RYTHMOL is not recommended for use in patients with less every property of the arrival reserved to the property of the pr with less severe ventricular arrhythmias, even if the patients are symptomatic. Use of RYTHMOL for the treatment of sustained ventricular tachycardia, like other antiarrhythmics,

CONTRAINDICATIONS

RYTHMOL (propafenone HCI) is contraindicated in the presence of uncontrolled congestive heart failure, cardiogenic shock, sinoatrial, atrioventricular and intraventricular disorders of impulse generation and/or conduction (e.g., sick sinus node syndrome, atrioventricular block) in the absence of an artificial pacemaker, bradycardia, marked hypotension, bronchospastic disorders, manifest electrolyte imbalance, and known hypersensitivity to the drug.

Mortality: In the National Heart Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a longterm, multicenter, randomized, double blind study in patients with asymptomatic non life threatening ventricular ectopy who had a myocardial infarction more asymptomatic non life threatening ventricular ectopy who had a myocardial infarction more than six days but less than two years previously and demonstrated mild to moderate left ventricular dysfunction, an excessive mortality or nonfatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730) compared with that seen in patients assigned to carrefully matched placebo treated groups (22/725). The average duration of treatment with encainide or flecainide in this study was ten months. The applicability of these results to other populations (e.g., those without recent myocardial infarction and to other antiarrhythmic drugs) is uncertain, but at present it is prudent (1) to consider any IC agent (especially one documented to provoke new serious arrhythmias) to have a similar risk and (2) to consider the risks of Class IC agents, coupled with the lack of any evidence of improved survival, generally unacceptable in patients without life threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life threatening, symptoms or signs.

arrhythmias, even if the patients are expensions.

Proarrhythmic Effects
RYTHMOL, like other antiarrhythmic agents, may cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., the severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., the severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., the severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., the severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., the severe ventricular tachycardia ventricular fibrillation or torsade de pointes; i.e., the severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., the severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., the severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., the severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., the severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., the severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., the severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., the severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., the severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., the severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., the severe ventricular tachycardia ventricular fibrillation or torsade de pointes; i.e., the severe ventricular tachycardia ventricular fibrillation or torsade de pointes; i.e., the severe ventricular tachycardia ventricular fibrillation or torsade de pointes; i.e., the severe ventricular tachycardia ventricular fibrillation or torsade de pointes; i.e., th tachycardia that is more sustained or more rapid which may lead to fatal consequences. It is therefore essential that each patient given RYTHMOL be evaluated electrocardiographically and clinically prior to, and during therapy to determine whether the response to RYTHMOL (propafenone HCI) supports continued treatment.Overall in clinical trials with propafenone. 4.7% of all patients had new or worsened ventricular arrhythmia possibly representing a proarrhythmic event (0.7% was an increase in PVCs; 4.0% a worsening, or new appearance, of VT or VF). Of the patients who had a worsening of VT (4%), 92% had a history of VT and/or VTV/T, 71% had coronary artery disease, and 68% had a prior myocardial infarction. The incidence of proarrhythmia in patients with less serious or benign arrhythmias, which include patients with an increase in frequency of PVCs, was 1.6%. Although most proarrhythmia events occurred during the first week of the proposition of the programme of the proposition of the proposition of the programme of the proposition of the propos proarrhythmic events occurred during the first week of therapy, late events also were seen and the CAST study (see above) suggests that an increased risk is present throughout

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)

PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE
PROPAFENONE or other agents with beta adrenergic blocking activity.

Congestive Heart Failure

Congestive Heart Failure
During treatment with oral propafenone in patients with depressed baseline function (mean EF=33.5%), no significant decreases in ejection fraction were seen. In clinical trial experience, new or worsened CHF has been reported in 3.7% of patients; of those 0.9% were considered probably or definitely related to RYTHMOL. Of the patients with congestive heart failure probably related to propafenone, 80% had preexisting heart failure and 85% had coronary artery disease. CHF attributable to RYTHMOL developed rarely (<0.2%) in patients who had no previous history of CHF. As RYTHMOL exerts both beta blockade and a (dose related) negative inotropic effect on cardiac muscle, patients with congestive heart failure should be fully compensated before receiving RYTHMOL. If congestive heart failure worsens, RYTHMOL should be discontinued (unless congestive heart failure is due to the cardiac arrhythmia) and, if indicated, restarted at a lower dosage only after adequate cardiac compensation has been established.

Conduction Disturbances

**Conduction Disturbances** 

PRYTHMOL slows atrioventricular conduction and also causes first degree AV block. Average PR interval prolongation and increases in QRS duration are closely correlated with dosage increases and concomitant increases in propafenone plasma concentrations. The incidence of first degree, second degree, and third degree AV block observed in 2,127 patients was 2.5%, 0.6%, and 0.2%, respectively. Development of second or third degree AV block requires a reduction in dosage or discontinuation of RYTHMOL. Bundle branch block (1.2%) and intraventicular conduction delay (1.1%) have been reconstitute activities received. and intraventricular conduction delay (1.1%) have been reported in patients receiving propafenone. Bradycardia has also been reported (1.5%). Experience in patients with sick sinus node syndrome is limited and these patients should not be treated with propafenone. Effects on Pacemaker Threshold

RYTHMOL may alter both pacing and sensing thresholds of artificial pacemakers Pacemakers should be monitored and programmed accordingly during therapy.

Hematologic Disturbances

Hematologic Disturbances

One case of agranulocytosis with fever and sepsis, probably related to use of propatenone, was seen in U.S. clinical trials. The agranulocytosis appeared after 8 weeks of therapy. Propatenone therapy was stopped and the white count had normalized by 14 days. The patient recovered. In the course of over 800,000 patient years of exposure during marketing outside the U.S. since 1978, seven additional cases have been reported. In one of these, concomitant captopril, a drug known to cause agranulocytosis, was used. Unexplained fever and/or decrease in white cell count, particularly during the first three months of therapy. warrant consideration of possible agranulocytosis/granulocytopenia. Patients should be instructed to promptly report the development of any signs of infection such as fever, sore

Hepatic Dysfunction:
Propatenone is highly metabolized by the liver and should, therefore, be administered cautiously to patients with impaired hepatic function. The dose of propafenone given to patients with impaired hepatic function should be significantly reduced. Careful monitoring for excessive pharmacological effects (see OVERDOSAGE) should be carried out.

Renal Dysfunction:

A considerable percentage of propafenone metabolites (18.5%-38% of the dose/48 hours) are excreted in the urine. Until further data are available, RYTHMOL should be administered

cautiously to patients with impaired renal function. These patients should be carefull signs of overdosage (see OVERDOSAGE)

Positive ANA titers have been reported in patients receiving proparenone. Patients wh develop an abnormal ANA test should be carefully evaluated and, if persistent or worsenin elevation of ANA titers is detected, consideration should be given to discontinuing therapy. Impaired Spermatogenesis:

Reversible disorders of spermatogenesis have been demonstrated in monkeys, dogs and rabbits after high dose intravenous administration. Evaluation of the effects of short term propafenone administration on spermatogenesis in 11 normal subjects suggests that propafenone produced a reversible, short term drop (within normal range) in sperm count subsequent evaluations in 11 patients receiving propafenone chronically have suggested not support the propagation of the p

effect of propatenone on sperm count

Drug Interactions: Quinidine: Small doses of quinidine completely inhibit the hydroxylation metabolic pathway, making all patients, in effect, slow metabolizers. There is, as yet, too little information to recommend concomitant use of propafenone and quinidine. Local information to recommend concomitant use of propafenone and quinidine. Loca Anesthetics: Concomitant use of local anesthetics may increase the risks of central nervous system side effects. Digitalis: RYTHMOL produces dose related increases in serum digoxin levels ranging from about 35% at 450 mg/day to 85% at 900 mg/day propafenone without affecting digoxin renal clearance. Digoxin dosage should ordinarily be reduced when propafenone is started. Beta-Antagonists: Propafenone appears to inhibit the hydroxylation pathway for propranoiol and metoprolol (just as quinidine inhibits propafenone metabolism). While the therapeutic range for beta-blockers is wide, a reduction in dosage may be necessary during concomitant administration with propafenone. Warfarin: In a study of eight healthy subjects receiving propafenone and warfarin concomitantly, mean steady-state warfarin plasma concentrations increased 39% with a corresponding increase in warfarin plasma concentrations increased 39% with a corresponding increase in prothrombin times of approximately 25%. It is therefore recommended that prothrombin times be routinely monitored and the dose of warfarin be adjusted if necessary. Cimetidine: Concomitant administration of propatenone and cimetidine in 12 healthy subjects resulted in a 20% increase in steady-state plasma concentrations of propatenone with no detectable changes in electrocardiographic parameters beyond that measured on propatenone alone. Other: Limited experience with propatenone combined with calcium antagonists and

Other: Limited experience with propatenone combined with calcium antagonists and diuretics has been reported without evidence of clinically significant adverse reactions. Carcinogenesis, Mutagenesis, Impairment of Fertility: Life time maximally tolerated oral dose studies in mice (up to 360 mg/kg/day) and rats (up to 270 mg/kg/day) provided no evidence of a carcinogenic potential for propatenone. RYTHMOL was not mutagenic when assayed for genotoxicity. Pregnancy Teratogenic Effects: Pregnancy Category C.: Propatenone has been shown to be embryotoxic in rabbits and rats when given in doses 10 and 40 times, respectively, the maximum recommended human dose. No teratogenic potential was apparent in either species. There are no adequate and well controlled studies in pregnant women. Propatenone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pregnancy Nonteratogenic Effects: In a perinatal and postnatal study in rats, propatenone, at dose levels of 6 or more times the maximum recommended human dose, produced dose dependent increases in maternal and neonatal mortality, decreased maternal and pup body weight gain and reduced neonatal physiological development. Labor and Delivery: It is not known whether the use of propatenone during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetrical intervention. Nursing Mothers: It is not known whether this drug is excreted in human milk and because of the potential for serious adverse reactions in nursing infants from RYTHMOL, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. drug to the mother

Grup to the mother.

Pediatric Use: The safety and efficacy of RYTHMOL in children has not been established.

Geriatric Use: There do not appear to be any age-related differences in adverse reaction rates in the most commonly reported adverse reactions. Because of the possible increased risk of impaired hepatic or renal function in this age group, RYTHMOL should be used with caution. The effective dose may be lower in these patients.

ADVERSE REACTIONS

Adverse reactions associated with RYTHMOL (propatenone HCI) occur most frequently in the gastrointestinal, cardiovascular, and central nervous systems. About 20% of patients discontinued due to adverse reactions.

Adverse reactions reported for ≥1% of 2.127 patients who received propafenone in U.S. clinical trials are presented in the following list. Dizziness, Nausea and/or Vomiting, Unusual Taste, Constipation, Fatigue, Dyspnea, Proarrhythmia, Angina, Headache(s), Blurred Vision, CHF, Ventricular Tachycardia, Dyspepsia, Palpitations, Rash, First Degree AV Block, Diarrhea, Weakness, Dry Mouth, Syncope/Near Syncope, Increased QRS Duration, Chest Pain, Anorexia, Abdominal Pain/Cramps, Ataxia, Insomnia, Premature Ventricular Contraction(s), Radden Target (Appl.) (Progress) (Pro Bradycardia, Anxiety, Edema, Tremor(s), Diaphoresis, Bundle Branch Block, Drowsiness, Atrial Fibrillation, Flatulence, Hypotension, Intraventricular Conduction Delay, Joint(s) Pain. In addition, the following adverse reactions were reported less frequently than 1% either in In addition, the following adverse reactions were reported less frequently than 1% either in clinical trials or in marketing experience (adverse events for marketing experience are given in italics). Causality and relationship to propafenone therapy can not necessarily be judged from these events. Cardiovascular System: Atrial flutter, AV dissociation, cardiac arrest, flushing, hot flashes, sick sinus syndrome, sinus pause or arrest, supraventricular tachycardia. Nervous System: Abnormal dreams, abnormal speech, abnormal vision, apnea, coma, confusion, depression, memory loss, numbness, paresthesias, psychosis/mania, seizures (0.3%), tinnitus, unusual smell sensation, vertigo. Castrointestinal: A number of patients with liver abnormalities associated with propafenone therapy have been reported in foreign postmarketing experience. Some appeared due to hepatocellular injury, some were cholestatic and some showed a mixed picture. Some of these reports were simply discovered through clinical symmistries, others because of clinical symmions. One case was discovered through clinical chemistries, others because of clinical symptoms. One case was rechallenged with a positive outcome. Cholestasis (0.1%), elevated liver enzymes (alkaline phosphatase, serum transaminases) (0.2%), gastroenteritis, hepatitis (0.03%) **Hematologic**. Agranulocytosis, anemia, bruising, granulocytopenia, *increased bleeding time*, leukopenia, purpura, thrombocytopenia. **Other:** Alopecia, eye irritation, hyponatremia/inappropriate ADH secretion, impotence, increased glucose, kidney failure, positive ANA (0.7%), lupus enthematics; muscle cramps, muscle verafices, particular in protection and control of the con matosis, muscle cramps, muscle weakness, nephrotic syndrome, pain, pruritus OVERDOSAGE

The symptoms of overdosage, which are usually most severe within 3 hours of ingestion, may include hypotension, somnolence, bradycardia, intraatrial and intraventricular conduction disturbances, and rarely convulsions and high grade ventricular arrhythmias. Defibrillation as well as infusion of dopamine and isoproterenol have been effective in controlling rhythm and blood pressure. Convulsions have been alleviated with intravenous General supportive measures such as mechanical respiratory assistance and external cardiac massage may be necessary.

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# Effective Antiarrhythmic Therapy with a Unique Pharmacologic Profile

**Excellent V-Tach efficacy:** <u>Rythmol</u> provided effective suppression of VT beats in patients with either sustained or non-sustained VT.

**Safety Profile:** 3.6% discontinuance due to cardiac and 1.9% or less discontinuance due to non-cardiac side effects at 450 mg/day (N = 1430).

**Beta Blocker Activity:** equal to 1/40th of propranolol. Patients with bronchospastic disease should, in general, not receive propafenone.

Available in 150 mg and 300 mg scored tablets.

Rythmol 150mg
Rythmol 150mg
#100
Sig. I tablet
Sig. T.D.

# **Recommended Dosage**

Begin therapy with <u>Rythmol</u> 150 mg t.i.d. (450 mg/day)

Increase to 225 mg t.i.d. (incremental increases can be implemented after 3 or 4 days) (675 mg/day)

If necessary increase to 300 mg t.i.d. (Maximum recommended dose 900 mg per day)



# Antihypertensive Effect of Isradipine Administered Once or Twice Daily on Ambulatory Blood Pressure

Yves Lacourcière, MD, Luc Poirier, LPhM, Danielle Dion, MD, and Pierre Provencher, PhD

The antihypertensive efficacy of sustained-release isradipine administered once daily compared to the immediate-release formulation administered twice daily was assessed by ambulatory blood pressure (BP) monitoring in a double-blind randomized crossover study in 76 mild-to-moderate hypertensive patients. Conventional BP and heart rate parameters were evaluated after a 4-week placebo period and patients qualified for entry if sitting diastolic BP was between 95 and 114 mm Hg. Ambulatory BP monitoring was measured at baseline and after active treatment with both formulations. The 2 regimens induced a significant and almost identical reduction (p <0.001) in the mean 24-hour BP without affecting heart rate. Isradipine was more effective in patients whose clinical hypertension was confirmed by ambulatory BP monitoring (35) than in patients who remained normotensive by ambulatory BP monitoring criteria (41). The isradipine-treated ambulatory hypertensive group experienced significantly greater decreases in BP during 24-hour, work, awake and sleep periods than did the ambulatory normotensive group. These data suggest that sustained-release isradipine has a sustained antihypertensive effect throughout 24 hours comparable to that of isradipine given twice daily and may improve compliance with long-term treatment. In addition, the results confirm the usefulness of ambulatory BP monitoring in determining truly hypertensive patients likely to respond to drug administration.

(Am J Cardiol 1990;65:467-472)

alcium antagonists are increasingly used for the treatment of hypertensive patients. 1-4 Isradipine, a new dihydropyridine derivative, has been shown to have potent calcium antagonistic properties in experimental studies. 5.6 Clinical experience with isradipine has demonstrated its antihypertensive efficacy when administered twice daily in a number of studies. 7-10 A sustained-release formulation has now been developed to facilitate once-a-day therapy in hypertension. Numerous studies have confirmed the usefulness of ambulatory blood pressure (BP) monitoring in the evaluation and treatment of patients with systemic hypertension. 11-14

A multicenter study of the antihypertensive effects of isradipine using the sustained-release formulation once a day provided the opportunity at 1 center to compare the magnitude of effect in lowering 24-hour ambulatory BP of this new formulation with the immediate-release compound given twice daily. In addition, we evaluated whether there were differences in the effects of isradipine between patients with hypertension defined by ambulatory BP monitoring and those who are normotensive according to 24-hour ambulatory monitoring criteria.

## **METHODS**

Patient population: Previously treated and newly diagnosed, untreated outpatients of both sexes between 20 and 70 years of age with mild-to-moderate essential hypertension were eligible for inclusion. In all patients secondary causes of hypertension were ruled out by routine screening tests. Informed consent was obtained from each participant and the study was approved by the local hospital ethics committee. Exclusion criteria included cerebral or myocardial infarction within the last 6 months, insulin-dependent diabetes mellitus, congestive heart failure, angina pectoris, bradycardia, second- or third-degree atrioventricular block, renal impairment, history of drug hypersensitivity, collagen diseases and childbearing potential. Concomitant medication known to interfere with the study medication was not permitted. In all patients previous therapy was discontinued for at least 4 weeks before the beginning of the study.

**Trial design:** After inclusion in the study the patients entered a 4-week single-blind placebo run-in period. Patients with the mean of 2 seated diastolic blood BPs between 95 and 114 mm Hg on the final day of the placebo period were randomized in a double-blind fashion to treatment with either isradipine 2.5 mg twice daily or sustained-release isradipine 5 mg once daily.

From the Hypertension Research Unit, Centre Hospitalier Université, Laval, Quebec, Canada. This study was supported by a grant from Sandoz Canada Inc., Montreal, Canada. Manuscript received September 6, 1989; revised manuscript received and accepted October 19, 1989.

Address for reprints: Yves Lacourcière, MD, Centre Hospitalier de l'Université Laval, 2705, Boulevard Laurier, Ste-Foy, Canada G1V 4G2.

Active treatment and placebo tablets were identical and patients were not aware that their treatment was being changed. Four weeks later, patients with normalized BP (seated diastolic BP <90 mm Hg) crossed over for another 4 weeks to the alternative isradipine formulation. For patients who remained hypertensive, the dose of isradipine was increased to either 5 mg twice daily or 10 mg once daily for another 4 weeks. After titration these patients were given the alternative treatment regimen for 4 additional weeks. Upon enrollment in the study patients were seen once every 2 weeks during placebo and active treatment periods. Visits were scheduled so that BP and pulse rate could be assessed approximately 12 hours after the evening dose of medication, which was 24 hours after the active dose of the sustained-release formulation.

Measurements: In-clinic BP was taken by the same trained observer with a standard mercury sphygmomanometer and using first and fifth Korotkoff sounds for

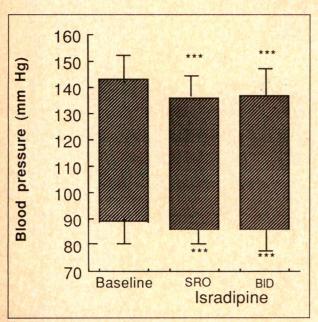


FIGURE 1. Effect of sustained-release or twice daily isradipine on ambulatory recorded blood pressure (BP). The BPs reflect the average of all readings taken during the monitoring, BID = twice daily: SRO = sustained-release, \*\*\*p <0.001 versus baseline.

systolic and diastolic BP, respectively. A long (18 × 88 cm) cuff with a 17 × 28 cm inflatable bladder was used in obese patients. BP was defined as the mean of 2 readings taken 2 minutes apart in the seated position after 15 minutes of rest. The results of the multicenter inclinic antihypertensive efficacy and safety assessment of sustained-release isradipine versus the twice-daily formulation will be reported separately.

Ambulatory BP was monitored with an automatic device (Spacelabs 92202, Spacelabs Inc.) in each patient at the end of the single-blind placebo period and after at least 4 weeks of double-blind therapy with each drug formulation at optimum dosage. All evaluations were done on a weekday and included working periods for patients employed outside the home. BP was recorded every 30 minutes during the working hours (from 8 A.M. to 6 P.M.) and every 60 minutes during the home period (7 P.M. to 7 A.M.). Patients were instructed to keep their arms still during BP measurements. When the instrumentation was fitted, the reliability of this device was cross-checked by the clinical observer with a standard mercury column sphygmomanometer on the contralateral arm. The correlation between the monitoring and the clinical observer was 0.94 for systolic BP and 0.89 for diastolic BP. Mean ambulatory BPs have been defined as an average of all nonartifactual measurements obtained during the 24-hour monitoring period. The values for each hour represent the averages of 2 measurements for each patient during the working period and 1 measurement during the home period.

Statistical analysis: The statistical analysis of the data was made using a crossover design at each time the data were sampled. 15 We performed analyses of the differences between the mean ambulatory BP of a subject during working or home periods while receiving placebo at baseline and during active treatment. Ambulatory measurements for each patient while receiving active treatment were taken twice, once on each formulation when the optimal dosage level was reached. The difference in hourly averages for drug versus placebo was established with a 1-way analysis of variance. The analysis of demographic data was made using a 1-way analysis of variance. Differences were considered significant when the p value was <0.05. Results are reported as mean ± standard deviation.

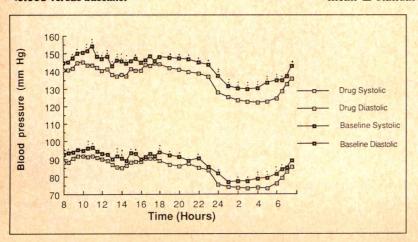


FIGURE 2. Mean hourly systolic and diastolic BPs before and during treatment with isradipine (5 to 10 mg/day) in 76 hypertensive patients. p <0.05; :p <0.01 versus baseline.

### RESULTS

Eighty-two white patients were recruited for the study, 6 of whom were withdrawn. Two patients were excluded during the placebo period because of poor compliance, and 2 patients were withdrawn during the active period because of ankle edema. One patient had a myocardial infarction and another patient was prescribed tricyclic antidepressant drugs by another physician. The final statistical evaluation included 76 patients who completed the 3 phases of the study and had 3 ambulatory BP monitorings. There were 41 men and 35 women aged 30 to 69 years (mean 51) with body weight of 47 to 94 kg (mean 74) and height between 146 and 167 cm (mean 177). History of hypertension varied from 1 month to 21 years (mean 8.2 years). Isradipine was taken at a final daily dose of 5 mg by 20 patients (10 men, 10 women) and 10 mg by 56 patients (31 men, 25 women). There were no significant differences betwen the groups receiving sustained-release isradipine or twice-daily isradipine in age, weight, height or duration of hypertension at entry in the trial. There was no significant change in body weight in either of the treatment groups during the trial.

Effectiveness of once- and twice-daily doses: Figure 1 shows the mean systolic and diastolic ambulatory BPs of all patients at baseline and while receiving isradipine. The mean 24-hour systolic and diastolic BPs were significantly (p <0.001) reduced by isradipine administered either once or twice daily without any difference between the formulations. Mean ambulatory BP was  $143/89 \pm 12/9$  mm Hg at the end of the placebo period and decreased to 137/85 ± 11/8 mm Hg during treatment with sustained-release isradipine and to 136/85 ± 11/9 mm Hg in response to isradipine twice daily. There was no difference in the ambulatory heart rate with either formulation compared to baseline. The mean 24-hour ambulatory heart rates were  $79 \pm 10$ beats/min at baseline, 80 ± 10 beats/min during treatment with isradipine sustained-release and  $79 \pm 9$ beats/min with isradipine twice daily.

The mean hourly ambulatory BPs of all 76 patients during the 24-hour monitoring are shown in Figure 2. Systolic BP was usually significantly lower during isradipine treatment than at baseline. Significant differences were less frequent for diastolic ambulatory BP during some hours of the working period. However, am-

FIGURE 3. Effects of isradipine therapy on 24-hour average BP and BP during work (8 A.M. to 6 P.M.), awake (6 A.M. to 10 P.M.) and sleep (11 P.M. to 5 A.M.) periods. P values (top) are for systolic BP and (bottom) diastolic BP.

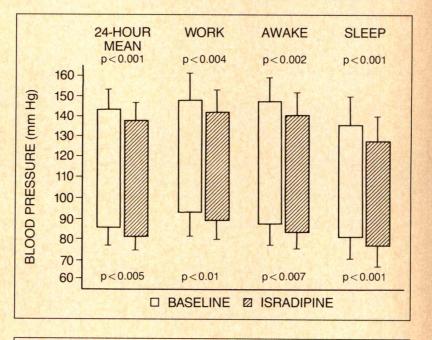


FIGURE 4. Mean hourly systolic and diastolic BPs during treatment with isradipine sustained release versus twice daily in hypertensive patients. b.i.d. = twice daily; o.d. = once daily.

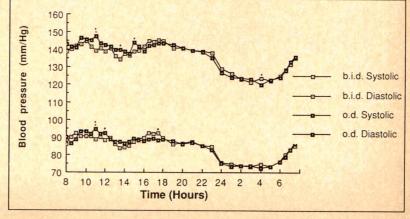


TABLE I Effects of Isradipine on Blood Pressure and Heart Rate in Ambulatory Hypertensive and Normotensive Patients

	SBP (mm Hg)	DBP (mm Hg)	HR (beats/min)
24-hr			
Hypertensive			
Baseline	151 ± 11	97 ± 5	80 ± 12
Isradipine	$142 \pm 10^{\ddagger}$	91 ± 6‡	81 ± 9§
Normotensive			
Baseline	$137 \pm 11$	83 ± 5	79 ± 8
Isradipine	133 ± 18*	80 ± 14§	78 ± 15 <sup>§</sup>
Work (8 A.M. to 6 P.M.)			
Hypertensive			
Baseline	155 ± 11	101 ± 6	$84 \pm 13$
Isradipine	147 ± 10 <sup>‡</sup>	95 ± 6‡	85 ± 10§
Normotensive			
Baseline	140 ± 12	86 ± 6	83 ± 9
Isradipine	136 ± 10§	84 ± 8§	83 ± 9§
Awake (6 A.M. to 10 P.M.)			
Hypertensive			
Baseline	154 ± 11	99 ± 6	82 ± 12
Isradipine	$145 \pm 10^{\ddagger}$	93 ± 6 <sup>‡</sup>	83 ± 10§
Normotensive			
Baseline	139 ± 11	85 ± 6	81 ± 8
Isradipine	135 ± 10§	83 ± 7§	81 ± 8§
Sleep (11 P.M. to 5 A.M.)			
Hypertensive			
Baseline	139 ± 12	86 ± 7	71 ± 11
Isradipine	130 ± 13 <sup>†</sup>	81 ± 8 <sup>†</sup>	71 ± 10 <sup>§</sup>
Normotensive			
Baseline	$103 \pm 17$	74±8	67 ± 8
Isradipine	122 ± 13 <sup>†</sup>	71 ± 7*	68 ± 7§

Data are mean  $\pm$  standard deviation.  $^{\circ}$  p <0.05,  $^{\circ}$  p <0.01,  $^{\circ}$  p <0.001 compared with baseline value;  $^{\circ}$  not significant. BP = blood pressure; D = diastolic; HR = heart rate;  $^{\circ}$  = systolic.

bulatory BP was significantly reduced during work (8 A.M. to 6 P.M.), awake (6 A.M. to 10 P.M.) and sleep (11 P.M. to 5 A.M.) periods (Figure 3). Moreover, while patients were receiving isradipine, the BP was lowered substantially over the whole circadian cycle (Figure 2). There was not a clear-cut difference between the 24hour BP profile obtained with isradipine once daily and that recorded while the patients were receiving isradipine twice daily (Figure 4). The mean hourly heart rate was not affected by isradipine administration (Figure 5) and no difference in heart rate was observed between isradipine given once or twice daily (data not shown).

Comparative changes in ambulatory blood pressure monitoring-defined hypertensive and normotensive patients: Analysis of the baseline 24-hour ambulatory BP values revealed that 35 patients (46%) were hypertensive based on the criterion of average whole-day diastolic BP ≥90 mm Hg, while 41 patients (54%) were normotensive by this criteria. The mean 24-hour ambulatory BP was  $150/97 \pm 10/5$  mm Hg for the hypertensive group versus  $137/83 \pm 10/5$  mm Hg for the normotensive group. The equivalent clinic BPs were 159/105 ± 14/5 mm Hg for the ambulatory BP monitoring-defined hypertensive patients and  $157/100 \pm 16/4$  mm Hg for the normotensive patients. The baseline heart rate was identical for both groups.

Table I compares the ambulatory BP reductions produced by isradipine administration during 24-hour, work, awake and sleep periods in normotensive and hypertensive patients. Both systolic and diastolic ambula-

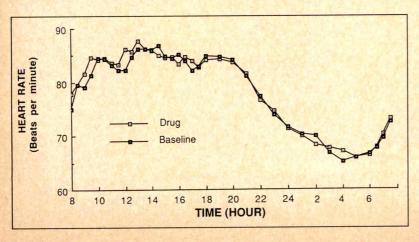


FIGURE 5. Mean hourly heart rate at baseline and during treatment with isradipine in 76 hypertensive patients.

tory BP were significantly reduced during every period in hypertensive patients. In contrast, both systolic and diastolic BPs were not significantly reduced by the calcium antagonist in normotensive patients during work and awake periods. A slight but significant reduction of systolic BP occurred during 24-hour and sleep periods. Diastolic BP was also reduced (p <0.05) during the sleep period.

When viewed on an hourly basis over 24 hours, further differences in BP were apparent. Automated ambulatory BP monitoring demonstrated that isradipine reduced systolic and diastolic ambulatory BPs almost every hour during whole-day monitoring in hypertensive (Figure 6) but not in normotensive (Figure 7) patients. The most marked reduction in systolic and diastolic ambulatory BPs in hypertensive patients occurred at work and during sleep. Moreover, the blood pressure was lowered substantially during the whole circadian cycle (Figure 6).

### DISCUSSION

The results of this study demonstrate that isradipine sustained-release is as effective as isradipine twice daily in lowering mean 24-hour ambulatory BP without increasing heart rate and that both formulations are significantly better than placebo. The ambulatory BP profiles recorded at the end of each treatment were similar. Moreover, our data suggest that isradipine is effective for 24 hours with significant reductions in BP during work, awake and sleep periods. These findings may be

relevant since ambulatory BP during work and during sleep cycles has been shown to be an important predictor of hypertensive heart diseases. <sup>16-18</sup> This information is important, since recent studies revealed that nitrendipine, another dihydropyridine calcium antagonist, was not effective in lowering work BP. <sup>19-21</sup> Moreover, another study<sup>22</sup> showed that tiapamil, an agent structurally similar to verapamil, did not produce any significant changes in 24-hour BP readings. In contrast to these studies, both systolic and diastolic BPs were significantly lowered during 24-hour, work, awake and sleep periods in our trial.

The second outcome of interest in this study, as shown previously<sup>13</sup> in another setting, was that ambulatory BP monitoring provided a more realistic evaluation of BP than the in-clinic BP in our patients. Using the criteria suggested by Weber et al,13 who demonstrated these differences, only 46% of our patients were found to be hypertensive during ambulatory BP monitoring. Our data confirmed those reported in a recent study<sup>23</sup> in which only 46% of 638 patients were diagnosed as hypertensive by ambulatory BP. However, these findings are in contrast to those of other investigators<sup>24-26</sup> who observed that 20 to 40% of individuals with office hypertension appear to be normotensive when studied by ambulatory monitoring. The reasons for these different findings are not immediately obvious; however, all studies show that a proportion of patients appearing to be hypertensive in the clinic are really normotensive if followed for a 24-hour period.

FIGURE 6. Mean hourly systolic and diastolic blood pressures (BPs) at baseline and during treatment with isradipine (5 to 10 mg/day) in 35 ambulatory hypertensive patients (mean 24-hour BP ≥90 mm Hg). ·p <0.05; :p <0.01 versus baseline.

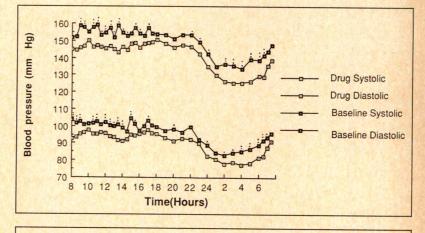
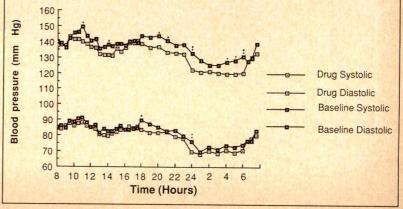


FIGURE 7. Mean hourly systolic and diastolic BPs at baseline and during treatment with isradipine (5 to 10 mg/day) in 41 ambulatory normotensive patients (mean 24-hour BP <90 mm Hg). ·p <0.05; :p <0.01 versus baseline.



Another important feature of this study was the confirmation of a different effect of response to antihypertensive therapy among patients diagnosed as hypertensive by 24-hour ambulatory measurement and those in whom hypertension was not apparent. We demonstrated that the antihypertensive effects of isradipine are more pronounced and sustained in patients whose average 24-hour diastolic BP was ≥90 mm Hg. This differential response is comparable to the response to diltiazem observed in a recent study by Weber et al<sup>13</sup> and has been discussed by Kaplan<sup>27</sup> in a review of calcium antagonists. Our finding reinforces the usefulness of ambulatory BP measurement in determining patients most likely to respond to antihypertensive drug treatment.

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# Percutaneous Double Balloon Valvotomy for Severe Rheumatic Mitral Stenosis

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Percutaneous double balloon valvotomy for severe rheumatic mitral stenosis was successfully performed in 281 of 285 consecutive patients. The changes evoked were a decrease of the mean transvalvular gradient from  $16 \pm 7$  to  $5 \pm 3$  mm Hg, an increase in cardiac output from 3.8  $\pm$  1.0 liters/min to 5.4  $\pm$  1.5 liters/min and an increase in mitral valve area from 0.86  $\pm$  0.24 cm<sup>2</sup> to 2.41  $\pm$  0.54 cm2. The mean pulmonary artery pressure decreased from 37  $\pm$  13 mm Hg to 27  $\pm$  12 mm Hg and the pulmonary vascular resistance decreased from 307  $\pm$  181 to 238  $\pm$  122 dynes/s/cm $^{-5}$ . Symptomatic improvement occurred in 272 of the 285 (95%) patients. There were 3 procedure-related deaths (1%). Postdilatation mitral regurgitation was not significant in most patients. Therefore, this procedure can be performed at a low risk with effective results and a fast recovery.

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urgical commissurotomy is an established treatment for mitral stenosis (MS). Nonsurgical balloon valvotomy for rheumatic MS was first reported by Inoue et all in 1984. Since then, balloon valvotomy has emerged as an alternative treatment. We feel our series of 285 double balloon valvotomy patients will help clarify the short-term hemodynamic response and complications of percutaneous mitral valvotomy. This study defines the success rate, short-term hemodynamic results and complications in 285 patients with symptomatic, rheumatic MS who underwent percutaneous double balloon valvotomy.

### **METHODS**

Patients: From February 1986 through August 1989, 311 consecutive patients underwent percutaneous mitral balloon valvotomy and, of these, 285 were by the double balloon technique. This group was made up of 48 males and 237 females with a mean age of  $44 \pm 14$ years (range 14 to 83). The duration of symptoms ranged from 1 to 40 years. There were no patients in the New York Heart Association functional class I; 92 were in class II, 149 were in class III and 44 were in class IV. Atrial fibrillation was present in 95 patients. Patients with thromboembolic events of <6 months or those with documented left atrial thrombi were excluded. There were 9 patients who had cerebrovascular accidents ≥24 months before the procedure and 51 patients had undergone 1 or more previous surgical mitral commissurotomies. In 46 patients the pulmonary artery pressures were near-systemic. Significant (≥60% luminal stenosis) 2- or 3-vessel coronary artery disease was found in 38 patients. An ejection fraction <0.40 was present in 25 patients. We graded fluoroscopically the degree of valvular calcium from 1+ to 4+ (1+ being barely visible calcium, 4+ being dense valvular and subvalvular calcium). There were 199 patients with fluoroscopic evidence of valvular calcium. Eighty-two patients had 1+, 68 had 2+, 33 had 3+ and 16 had 4+ degree of calcium. The severity of mitral regurgitation was also graded on a 1+ to 4+ scale according to the degree of opacification of the left atrium and pulmonary veins during the left ventriculography.<sup>2,3</sup> There were 113 patients with 1+ and 39 with 2+ mitral regurgitation before the balloon valvotomy. Patients with 3+ or 4+ were exclud-

Valvotomy protocol: All patients were given the option of surgical valvotomy. Each patient gave special informed consent approved by our investigational review board committee. The same operators (CER and FYKL) were involved in all cases.

All patients taking oral anticoagulants had their warfarin discontinued at least 48 hours before the pro-

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cedure. Transseptal catheterization was accomplished from the right femoral vein using a modified Brockenbrough needle and an 8Fr Mullins transseptal sheath (USCI). Systemic anticoagulation was achieved with 150 IU/kg of heparin given after successful transseptal catheterization. The mean gradient across the mitral valve was measured with simultaneous thermodilution cardiac outputs.

A Lau-Ruiz exchange wire (Medrad Inc.) was advanced and placed at the apex of the left ventricle via the Mullins transseptal sheath. A 7Fr catheter with an initial diameter of 8 mm and a recent 6 mm diameter and a dilating balloon with a length of 3 cm (Meditech Inc.) were used for septostomy (Figure 1A and 1B). After septostomy the Mullins sheath was readvanced into the left ventricle and a second Lau-Ruiz exchange wire was advanced and positioned next to the first one. The transseptal sheath was then removed and the 2 valvotomy balloon catheters (Mansfield Scientific Inc.) were advanced over the wires and positioned across the mitral valve. The balloons were then simultaneously inflated by hand (Figure 1C) until the "waist" of the stenotic valve on the balloons disappeared (Figure 1D). Two to 4 inflations of 20 to 60 seconds on the average were done. The balloon length that was used ranged from 3 to 5.5 cm depending on the length of the left ventricular cavity. Balloons were chosen so that the sum of the 2 diameters was 10 to 37% larger than the anulus diameter (mean 26%).

Immediately after the balloon valvotomy, complete right- and left-sided heart pressures were obtained with simultaneous recording of the transvalvular gradient and cardiac outputs. Left atrial cineangiograms were filmed in the cranial left anterior oblique projection to evaluate the angiographic presence of a left to right shunt; oximetric studies were also done. Left ventriculography was performed to evaluate the severity of mitral regurgitation. Most of the patients were discharged from the hospital within 24 hours after the procedure.

If a significant left-to-right shunt occurred, a Fick cardiac output was performed. The mitral valve area was calculated by the standard Gorlin formula.

**Statistical analysis:** Data are expressed as the group mean ± standard deviation. Pre- and postdilatation comparisons were made using the Wilcoxon signed-ranks test and a p value <0.05 was considered indicative of a statistically significant difference; p values >0.05 are also given.

# RESULTS

The balloon catheters could not be passed across the valve in 5 of 285 patients. Three were not crossed because of heavy calcium (1 was successfully crossed on a second setting and the other 2 underwent elective mitral valve replacement). A patient had a septal tear during the atrial septostomy resulting in pericardial tamponade and 1 patient developed pericardial tamponade at the time of the transseptal puncture and underwent surgical drainage and a closed commissurotomy. Short-term complications in 5 more patients prevented measurement of postvalvotomy hemodynamics. The pre- and postvalvotomy hemodynamic results for the remaining 276 patients are listed in Table I. The hemodynamic improvement was accompanied by symptomatic improvement in 272 of the 285 patients (Figure 2).

Procedure tolerance and complications: Color-flow Doppler with 2-dimensional transesophageal echocar-diograms (Acuson-128, Acuson Co.) performed during

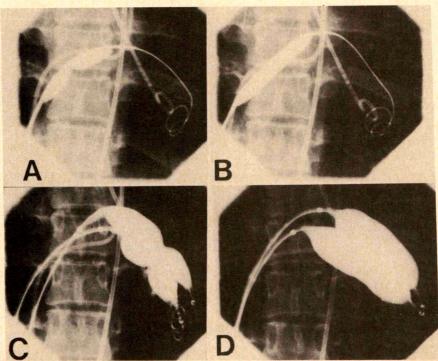


FIGURE 1. Anteroposterior view. A 6-mm diameter balloon being inflated across the interatrial septum (A) until the "waist" disappeared (B). Two balloons 20 mm in diameter by 4 cm in length being inflated across the stenotic mitral valve (C) until the "waist" disappeared (D).

inflation of both balloons across the mitral valve showed a clear flow channel by color Doppler between the anterior leaflet of the mitral valve and the balloons (Figure 3). Left ventriculography to assess mitral regurgitation pre- and postvalvotomy was available in 278 cases. One hundred seventeen of these patients showed no change, 131 showed an increase of 1 grade and 12 experienced an increase of >1 grade. There were 2 patients (ages 21 and 23) who had no valvular calcium in whom the anterior mitral leaflet was ruptured, needing mitral valve replacement. Another patient developed 4+ mitral regurgitation and underwent mitral valve repair of a torn anterior leaflet. A fourth patient who had end-stage MS and developed 3+ mitral regurgitation refused surgery, remained in functional class IV and died of pneumonia and sepsis 45 days later. In 18 patients the degree of mitral regurgitation either improved or disappeared (Figure 4).

Oximetric studies and left atrial angiograms after the percutaneous double balloon valvotomy revealed a

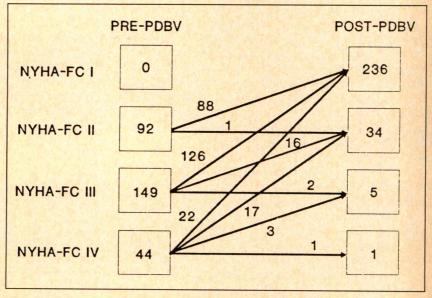
**TABLE I** Hemodynamic Results Following Percutaneous Double Balloon Valvotomy

	Market State of the State of th		
产生的 医红色	Pre-PDBV	Post-PDBV	p Value
Mean transvalvular gradient (mm Hg)	16 + 7	5+3	<0.00001
Cardiac output (liters/min)	3.8 + 1.0	5.4 + 1.5	< 0.0001
Mitral valve area (cm <sup>2</sup> )	0.86 + 0.24	2.41 + 0.54	< 0.0001
Mean pulmonary artery	37 + 13	27 + 12	< 0.0005
pressure (mm Hg)			
Left atrial pressure (mm Hg)	27 + 8	16+6	< 0.0001
Pulmonary vascular resistance	307 + 181	238 + 122	< 0.005
(dynes/s/cm <sup>-5</sup> )			

PDBV = percutaneous double balloon valvotomy

small left-to-right shunt at the atrial septostomy level in 39 patients (14%). In only 6 patients, the pulmonary to systemic flow ratio was between 1.5:1 and 2:1. No patient required surgical intervention for the shunt. One patient developed a transient Mobitz II second-degree heart block (30 minutes). Traumatic pericardial effu-

FIGURE 2. Changes of New York Heart Association functional class (NYHA-FC) after percutaneous double balloon valvotomy.



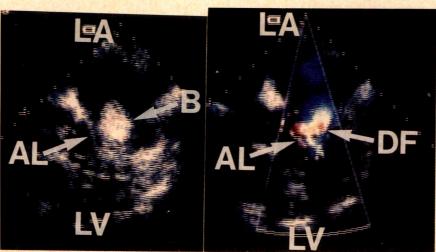


FIGURE 3. Transesophageal 2-dimensional echocardiogram and color flow Doppler in a patient undergoing percutaneous double balloon valvotomy. *Left*, both balloons inflated across the mitral valve. *Right*, the color flow Doppler shows a mosaic color pattern indicating a high velocity flow between both balloons during inflation. AL = anterior leaflet; B = balloons; DF = diastolic flow; LA = left atrium; LV = left ventricle.

sion during the transseptal approach occurred in 9 patients. Two of the 9 required surgical evacuation, 4 had successful valvotomy at the same setting, 2 had successful valvotomy 48 to 72 hours later and one had a successful valvotomy 4 weeks later.

Two patients developed transient ischemic attacks at the end of the procedure and recovered completely in 4 to 6 hours. Serial computerized axial tomography brain scans were normal. A third patient developed a similar episode 18 hours after being discharged from the hospital, and her neurologic deficit returned 4 hours later, and a fourth patient sustained a small embolic cerebrovascular accident with residual left lower extremity weakness. All these patients were in sinus rhythm without documented atrial fibrillation and were not anticoagulated before the procedure.

There were 5 left ventricular perforations and all 5 patients underwent emergency thoracotomy. However, one of them, due to prolonged cardiopulmonary resuscitation, sustained extensive anoxic encephalopathy and died 5 weeks later. The second death was in an 83-year-old patient who had concomitant severe aortic stenosis (aortic valve area of 0.4 cm²) and severe 3-vessel coronary artery disease. This patient also sustained a left ventricular perforation and did not survive the attempted operative repair. Two patients recovered uneventfully from their left ventricular perforation and the fifth patient left the hospital with some lack of memory due to a mildly anoxic brain. She remains asymptomatic of mitral valve disease (overall mortality of 1%).

### DISCUSSION

Several investigators have demonstrated the efficacy of percutaneous balloon mitral valvotomy by different techniques. We believe the double balloon technique has a geometric advantage over the single balloon technique. This advantage relates to the area and diameter. Two balloons with the same diameter have one-half the area when compared to a single balloon of the same diameter. The practical advantage of this is 2-fold.

First, with less area occupied, there is more room for blood to pass around the balloons as demonstrated in our laboratory by transesophageal 2-dimensional echocardiography (Figure 3). Secondly, the most effective dimension in valve dilatation is the long diameter of the elliptical valvular shape, since this produces the commissural separation. We believe this oversizing approach produces greater commissural separation giving larger valve areas.

The hemodynamic response of our patients to valvotomy showed a greater increase in cardiac output compared to other investigators. 6-11 A similarity in the pressures led to a greater increase in valve area in our group when compared to other reports. 6-11 The higher cardiac output noted could be related to the use of different equipment, larger atrial septal defects or larger valve areas. It is unlikely that equipment differences account for our higher values since we have performed our studies in many laboratories using different equipment with similar results in each laboratory. Our estimates of septal shunting by oximetries are similar to the results others have reported<sup>8,10</sup>; therefore we believe our patients actually achieved larger valve areas. This might occur if our patients had more pliable valves than other patients studied previously or if our technique of oversizing the anulus diameter resulted in larger valve areas after valvotomy. We feel the latter 2 factors best explain the greater improvement in our patients' valve areas.

**Complications:** In most patients balloon septostomy leaves an atrial septal defect that is of no hemodynamic significance. In our series, 39 patients had angiographic evidence of left-to-right shunt; however, only 6 of these patients had a Qp/Qs >1.5:1, and none had a Qp/Qs >2:1. There have been reports of hemodynamically significant left-to-right shunts after percutaneous valvotomy with a Qp/Qs >1.5:1.9 These investigators used a larger single balloon (25 mm). The larger balloon may account for a larger interatrial communication. Another factor that may lead to a larger shunt is a greater residual MS. In our series the 4 patients who had a iatrogen-

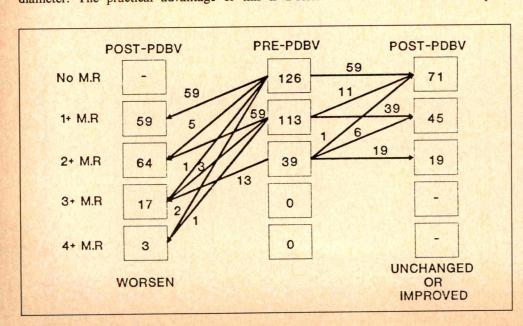


FIGURE 4. Changes in degree of mitral regurgitation in 278 patients before and after effective percutaneous double balloon valvotomy (PDBV) as assessed by angiography. MR = mitral regurgitation.

ic atrial septal defect with a Qp/Qs >1.5:1 were among the patients with lowest postdilatation mitral valve areas (1.4 to 1.6 cm<sup>2</sup>). The key issues in the degree of atrial septal defect will be how successful the mitral valvotomy is, how much the left atrial pressure is reduced and what the profile is of the balloons introduced across the septum.

Four of our patients (1.4%) developed transient or permanent cerebral ischemic attack, presumably from an embolic event. The 4 patients were in normal sinus rhythm without evidence of previous episodes of atrial fibrillation. We now recommend oral anticoagulation in all patients, regardless of their rhythm, for at least 6 to 8 weeks before and for another 6 to 8 weeks after mitral valvotomy. Transesophageal 2-dimensional echocardiography allows us to image the atrial appendage and has helped identify a greater number of patients with thrombi that may decrease the risk of emboli.

Left ventricular perforation was involved in 2 of the 3 deaths. We think that this complication can be reduced, if not abolished, by using differently designed balloon catheters. The occurrence of acute complications with the present technology convinced us that surgical stand-by is essential for all mitral valvotomies.

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# Prognostic Significance of Radionuclide-Assessed Diastolic Function in Hypertrophic Cardiomyopathy

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To evaluate the prognostic significance of diastolic function in hypertrophic cardiomyopathy (HC), technetium-99m gated equilibrium radionuclide angiography, acquired in list mode, was performed in 161 patients. Five diastolic indexes were calculated. During 3.0  $\pm$  1.9 years, 13 patients had disease-related deaths. With univariate analysis, these patients were younger (29  $\pm$  20 vs 42  $\pm$ 16 years; p <0.05), had a higher incidence of syncope (p <0.025), dyspnea (p <0.001), reduced peak filling rate (2.9  $\pm$  0.9 vs 3.4  $\pm$  1.0 end-diastolic volume/s; p = 0.09) with increased relative filling volume during the rapid filling period (80  $\pm$  7 vs 75  $\pm$  12%; p = 0.06) and decreased atrial contribution (17  $\pm$  7 vs 22  $\pm$  11%; p = 0.07). Stepwise discriminant analysis revealed that young age at diagnosis, syncope at diagnosis, reduced peak ejection rate, positive family history, reduced peak filling rate, increased relative filling volume by peak filling rate and concentric left ventricular hypertrophy were the most statistically significant (p = 0.0001) predictors of disease-related death (sensitivity 92%, specificity 76%, accuracy 77%, positive predictive value 25%). Discriminant analysis excluding the diastolic indexes, however, showed similar predictability (sensitivty 92%, specificity 76%, accuracy 78%, positive predictive value 26%). To obtain more homogenous groups for analysis, patients were classified as survivors (116) or electrically unstable (40), including sudden death, out-of-hospital ventricular fibrillation and nonsustained ventricular tachycardia during 48hour ambulatory electrocardiography, and heart failure death or cardiac transplant (5). None of the diastolic indexes achieved statistical differences between the groups. Radionuclide assessment of diastolic function in HC did not improve predictability for 3-year mortality or contribute to the identification of patients at increased risk of sudden death. (Am J Cardiol 1990:65:478-482) The natural history of patients with hypertrophic cardiomyopathy (HC) is premature cardiac death that is most often sudden. A major challenge in management is the identification of patients who are at increased risk. Although diastolic abnormalities are common in HC, their importance in relation to symptoms and prognosis has not been fully established. This study evaluates prospectively the prognostic significance of indexes of diastolic function derived from equilibrium radionuclide angiography in 161 patients with HC.

# **METHODS**

Patient selection: Patients were aged 8 to 78 years (mean 42); 6 were ≤14 years, 16 were >14 and ≤21 and the remaining 139 were >21 years; 90 were male and 71 female. The diagnosis of HC was based on the echocardiographic demonstration of unexplained left ventricular hypertrophy.<sup>6,7</sup> All patients had systolic and diastolic blood pressure <140 and <90 mm Hg, respectively. One hundred seventeen patients (73%) had asymmetric septal hypertrophy, 31 (19%) concentric hypertrophy and 13 (8%) distal hypertrophy according to the echocardiographic criteria described previously.<sup>7</sup> Thirty-five patients (22%) had complete systolic anterior motion of the mitral valve with septal contact. Left ventricular end-diastolic, end-systolic and left atrial dimensions were 42 ± 6, 26 ± 5 and 39 ± 8 mm, respectively.

Forty-eight-hour ambulatory electrocardiography was performed while patients were not receiving any cardiac medication at initial evaluation; 36 (22%) had nonsustained ventricular tachycardia of ≥3 beats at a mean rate of >120 beats/min.

Equilibrium radionuclide angiography: Fifty-eight patients (36%) underwent radionuclide angiography at the time of diagnosis. In the remainder, the mean time from diagnosis of HC to radionuclide examination was  $5.4 \pm 6.4$  years. All patients were in sinus rhythm at the time of radionuclide study; patients with moderate-to-severe mitral regurgitation were excluded. The examinations were performed while patients were not receiving any cardiac medication (73) and at least 18 hours after the cessation of  $\beta$  blockers or verapamil (53); 35 patients were receiving amiodarone at the time of the study.

Left ventricular systolic and diastolic function were assessed by R-wave gated equilibrium radionuclide angiography acquired in list mode. All studies were performed at rest in the supine position; cuff blood pressure

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**TABLE I** Diastolic Indexes Derived From Radionuclide Angiography in Patients with HC Versus Normal Subjects

	HC (n = 161)	Normal (n = 28)			
PFR (edv/s)	3.3 ± 1.0	3.0 ± 0.5	NS		
TPFR (ms)	$188 \pm 48$	$149 \pm 34$	< 0.001		
RFV1 (%)	$40 \pm 12$	$37 \pm 10$	NS		
RFV2 (%)	$76 \pm 12$	78 ± 9	0.16		
AC (%)	$21 \pm 11$	16±9	< 0.05		

AC = atrial contribution; edv = end-diastolic volume; HC = hypertrophic cardiomy-opathy; NS = not significant; PFR = peak filling rate; RFV1 = relative filling volume by peak filling rate; RFV2 = relative filling volume during the rapid filling period; TPFR = time to peak filling rate.

and heart rate were recorded after 10 to 15 minutes of rest before each study. After labeling of red blood cells in vivo using 15 mCi of technetium-99m,8 images were acquired using a large field-of-view rotating gamma cameras (General Electric Maxi 400T) and a medium sensitivity parallel hole collimator oriented in a 45° left anterior oblique projection with caudal tilt. Data were acquired from 600 to 900 consecutive cycles and stored in the computer (A2, Medical Data Systems) for subsequent analysis. An RR interval histogram was constructed and complexes falling outside an operatorselected range (± 10% from the mean RR interval) were rejected. A background-corrected composite left ventricular time-activity curve was then generated at a frame rate of 10 to 25 ms/frame by combined forward and reverse gating from the R wave.9

A standard count-based method was used for calculation of left ventricular ejection fraction. Peak rates of ejection and filling were derived as previously described. Time to peak filling rate was defined as the interval from the minimum of the curve to the point of peak filling (Figure 1). P.11

Diastasis was defined as 3 consecutive frames after the peak filling rate with <2% change in the left ventricular counts. Atrial contribution was considered to start when the rate of filling increased again after peak filling rate (Figure 2). Atrial contribution was measured in 140 (87%) patients; a maximum on the second derivative after peak filling rate did not occur in the remaining 21 patients (13%). The relative filling volumes by the time of peak filling rate, during the rapid filling period and during atrial contraction were calculated as a percentage of total left ventricular filling volume (Figure 1).

Twenty-eight apparently healthy volunteers aged 14 to 69 years (mean 39) served as normal control subjects for the radionuclide study. They were hospital workers and their relatives who had normal electrocardiograms and chest x-rays; 16 were men and 12 were women.

Statistical analysis: Results are expressed as mean ± 1 standard deviation. A Student t test was used to compare the means of the continuous variables and contingency tables were analyzed using a chi-square test. Linear discriminant analysis, with stepwise variable selection and Wilks' Lambda as the selection and optimization criteria, was used to assess the potential to predict disease-related death and electrical instability. A Bayes rule with equal prior probability was used for the predictions, and the results are presented as sensitivity,

**TABLE II** Clinical and Prognostic Features in 161 Patients with HC: Dead Versus Alive

100071110			
	Dead	Alive	
	(n = 13)	(n = 148)	p Value
Age at diagnosis (yrs)	21 ± 16	$37 \pm 17$	<0.005
Age at radionuclide examination (yrs)	$29 \pm 20$		< 0.005
Family history None	8	90	NS
HC	2	29	143
HC + sudden death	3	29	Mark (C)
Pattern of LVH ASH	8	109	NS
Concentric	4	27	143
Apical	1	12	
Systolic anterior motion	3	32	NS
of the mitral valve		02	
Clinical symptoms at diagnosis			
Angina None	8	87	NS
Atypical	1	11	
Exertional	3	36	
Exertional + atypical	1	14	E CLEAN
Dyspnea I	7	92	NS
	5	49	
III + IV	1	7	
Syncope None	6	109	<0.025*
Presyncope	0	10	<b>表示是原则是</b>
Syncope	7	29	
Clinical symptoms at the examination			A Control
Angina None	8	91	NS
Atypical	1	9	
Exertional	2	37	A STATE OF S
Exertional + atypical	2	11	
Dyspnea I	7	87	<0.001 <sup>†</sup>
	1	50	
III + IV	5	11	
Syncope None	8	120	<0.05*
Presyncope	0	10	
Syncope	5	18	
VT assessed ambulatory ECG	4	32	NS
Amiodarone therapy	6	47	NS

\* p value for no syncope versus presyncope and syncope; † p value for dyspnea I versus dyspnea II, III and IV (New York Heart Association functional class).

ASH = asymmetrical septal hypertrophy; ECG = electrocardiography; HC = hypertrophic cardiomyopathy; LVH = left ventricular hypertrophy; NS = not significant; VT = ventricular tachycardia.

**TABLE III** Radionuclide Cineangiography in 161 Patients with HC: Dead Versus Alive

	Dead (n = 13)	Alive (n = 148)	p Value
PFR (edv/s)	$2.9 \pm 0.9$	$3.4 \pm 1.0$	0.09
TPFR (ms)	201 ± 55	$185 \pm 47$	NS
RFV1 (%)	42 ± 15	$40 \pm 12$	NS
RFV2(%) (n = 140)	$80 \pm 7$	$75 \pm 12$	0.06
AC (%) (n = 140)	17 ± 7	22 ± 11	0.07
EF (%)	$71 \pm 15$	$77 \pm 10$	NS
PER (edv/s)	$3.6 \pm 0.9$	$4.1 \pm 0.9$	0.08

AC = atrial contribution; edv = end-diastolic volume; EF = ejection fraction; HC = hypertrophic cardiomyopathy; NS = not significant; PER = peak ejection rate; PFR = peak filling rate; RFVI = relative filling volume by peak filling rate; RFVI = relative filling volume to peak filling rate.

specificity, accuracy and positive predictive value. The computations were performed using the Statistical Package for the Social Sciences computer program for personal computers.

### RESULTS

The patients were followed  $3.0 \pm 1.9$  years after the radionuclide examination. During follow-up 13 patients had disease-related deaths. Of these, 5 died suddenly, 3

were resuscitated from out-of-hospital ventricular fibrillation, 4 died from heart failure and 1 patient required cardiac transplantation because of severe cardiac failure. Two patients underwent successful myotomy/myectomy, 72 received propranolol (mean dose 240 mg daily) and 9 had verapamil (mean dose 320 mg daily). Amiodarone was prescribed (mean dose 200 mg daily) for nonsustained ventricular tachycardia in 26, refractory symptoms in 14, paroxysmal atrial fibrillation in 12 and Wolff-Parkinson-White syndrome in 1 patient.

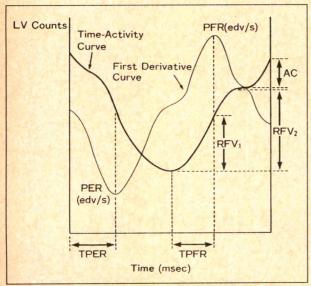


FIGURE 1. Calculation of peak rates of ejection and filling, time intervals and relative filling volumes from the radionuclide time-activity curve and its first derivative curve. Peak ejection and filling rates were normalized to end-diastolic counts and expressed as change from end-diastolic volume/s (edv/s). Time to peak filling rate (TPFR) was defined as the interval from end-systole (minimum of the curve) to the point of peak filling. Relative filling volume by peak filling rate (RFV<sub>1</sub>), relative filling volume during the rapid filling period (RFV<sub>2</sub>) and atrial contribution (AC) were defined as proportional filling volume at each point and were normalized to end-diastolic counts. LV = left ventricle; PER = peak ejection rate; TPER = time to peak ejection rate.

Radionuclide measurements: hypertrophic cardiomyopathy versus normal subjects: Five diastolic indexes were compared between HC and normal subjects (Table I). Time to peak filling rate was prolonged and atrial contribution was increased in patients with HC.

Univariate analysis for disease-related death: With univariate analysis, patients who had disease-related deaths were younger at the time of diagnosis and the time of radionuclide examination and more of them experienced syncope and more severe dyspnea (Table II), while radionuclide measurements revealed reduced peak ejection and peak filling rates and a greater percentage of filling during the rapid filling period (Table III).

Multivariate analysis for disease-related death: Eighteen of the 20 variables in Tables II and III were considered potential predictors for the occurrence of disease-related death during follow-up and entered into a stepwise discriminant analysis. Two diastolic indexes, relative filling volume during the rapid filling period and atrial contribution, were excluded from the analysis because these measurements could not be made in 21 patients. Multivariate analysis in 161 patients revealed that young age at diagnosis, syncope at diagnosis, reduced peak ejection rate, positive family history, reduced peak filling rate, increased relative filling volume by peak filling rate and concentric left ventricular hypertrophy were the most statistically significant (p = 0.0001) predictors of disease-related death. After excluding 21 patients without atrial contribution, the analysis was repeated in 140 patients using all 20 variables listed in Tables II and III, including relative filling volume during the rapid filling period and atrial contribution; sensitivity decreased by 12%, but specificity, accuracy and positive predictive value were similar (Table IV). When discriminant analysis was repeated without diastolic indexes and then without radionuclide indexes, overall predictability was similar (Table IV). The analysis was also repeated excluding 23 patients with ventricular tachycardia who were receiving amiodarone. Sixteen of the 18 variables used in the first multivariate analysis described above (ventricular tachycardia and

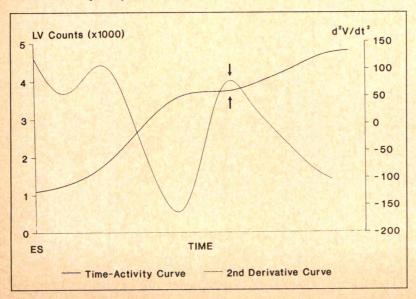


FIGURE 2. Method used to measure the contribution to filling by atrial contraction. Second derivative curve derived from the time-activity curve is analyzed. A maximum after peak filling rate is present on the second derivative curve (arrow) and corresponds to the inflection point (arrow) at which atrial contribution starts. ES = end-systole; LV = left ventricle.

TABLE IV Predictability for Disease-Related Death by Discriminant Analysis With or Without Radionuclide Indexes

	Sensitivity	Specificity	Accuracy	Predictive Value
With all radionuclide indexes (%)*	80	80	80	24
With all radionuclide indexes except for AC and RFV2 (%)†	92	76	77	25
Without diastolic indexes (%)†	92	76	78	26
Without radionuclide indexes (%)†	85	78	79	26

AC = atrial contribution; RFV2 = relative filling volume during the rapid filling period; Sensitivity = number of true positive detections/total number of positives in the group tested; Specificity = number of true normals detected/total number of normals in the group tested; Accuracy = number of true test results (true positives + true negatives)/total number of tests performed; Predictive Value = true positives/true positives + false positives.

\* Analysis was performed using 140 patients after excluding 21 patients without AC and RFV2.

† Analysis was performed using 111 patients.

amiodarone therapy were excluded) were entered into a stepwise discriminant analysis. The factors that were the most statistically significant (p <0.0001) predictors of disease-related death were young age at diagnosis, syncope at diagnosis, reduced peak ejection rate, dyspnea at the radionuclide study, positive family history and concentric left ventricular hypertrophy (sensitivity 77%, specificity 82%, accuracy 82%, positive predictive value 31%).

Univariate analysis for electrical instability: To possibly obtain more homogenous subsets for analysis, patients were classified as survivors, electrically unstable including sudden death, out-of-hospital ventricular fibrillation and nonsustained ventricular tachycardia during 48-hour ambulatory electrocardiography, and cardiac transplant or death from heart failure (Table V).

Peak ejection rate was significantly reduced in patients who died from cardiac failure or underwent cardiac transplantation but there were no other significant differences between the groups whether the nonsustained ventricular tachycardia/amiodarone patients were classified as survivors or as electrically unstable or were excluded from the analysis (Tables III and V).

Multivariate analysis for electrical instability: Sixteen of the 18 variables used in the first multivariate analysis described above were entered into a stepwise discriminant analysis that included data from 156 patients. Two variables, ventricular tachycardia and amiodarone therapy, and 5 patients, who died from cardiac failure or underwent cardiac transplantation, were excluded. The factors that were the most statistically significant (p <0.025) predictors of electrical instability were syncope at diagnosis, reduced peak ejection rate, positive family history and age at diagnosis and at the radionuclide study (sensitivity 60%, specificity 70%, accuracy 67%, positive predictive value 41%). The analysis was repeated in 136 patients using all 18 variables, after excluding the 25 patients who did not have the diastolic indexes of relative filling volume during the rapid filling period and atrial contribution, or who died from cardiac failure or underwent cardiac transplantation: sensitivity of 60%, specificity of 64%, accuracy of 63% and positive predictive value of 38% were similar.

### DISCUSSION

Diastolic abnormalities in HC have been characterized by angiography, 12-16 echocardiography/Doppler 17-<sup>22</sup> and radionuclide angiography. <sup>11,23-25</sup> In the present radionuclide study of 161 patients, time to peak filling

TABLE V Radionuclide Indexes Among Three Different Groups

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	Group 1 (n = 116)	Group 2 (n = 40)	Group 3 (n = 5)
PFR (edv/s)	$3.4 \pm 1.0$	$3.3 \pm 0.9$	2.4 ± 0.9*
TPFR (ms)	$187 \pm 46$	$186 \pm 47$	185 ± 84
RFV1 (%)	40 ± 11	40 ± 12	$34 \pm 14$
RFV2 (%) (n = 140)	$75 \pm 12$	$77 \pm 11$	77 ± 8
AC (%) (n = 140)	22 ± 12	$20 \pm 10$	$17 \pm 10$
EF (%)	$78 \pm 10$	76±9	61 ± 19
PER (edv/s)	$4.2 \pm 0.9$	$3.9 \pm 0.8$	$2.8 \pm 0.8^{\dagger}$

\* p <0.10; † p <0.025. AC = atrial contribution; edv = end-diastolic volume; EF = ejection fraction; Group 1 survivors without ventricular tachycardia; Group 2 = patients with ventricular achivors without verificular tachycardia; Group 2 = patients with ventricular tachycardia on 48 hour ambulatory electrocardiography, those experienced ventricular fibrillation or died suddenly; Group 3 = patients who died from heart failure or underwent cardiac transplantation; PER = peak ejection rate; PFR = peak filling rate; RFV1 = relative filling volume by peak filling rate; RFV2 = relative filling volume during the rapid filling period; TPFR = time to peak filling rate.

rate was prolonged and atrial contribution was increased compared to normal subjects. Bonow et al. 11,23-<sup>25</sup> also using radionuclide angiography, have reported similar findings of prolonged isovolumetric period and time to peak filling rate, reduced relative filling volume during the rapid filling period and increased atrial contribution in HC. The relation of diastolic abnormalities to clinical and prognostic features has not been extensively evaluated. In an angiographic study, Newman et al15 showed that patients who subsequently died suddenly had reduced peak ejection and reduced peak filling rates at the time of diagnosis when compared with survivors, whereas there were no differences between patients who died from other cardiac causes and survivors. Bonow et al<sup>24</sup> reported improved left ventricular diastolic filling and increased exercise tolerance in patients treated with verapamil, in association with an increase in peak filling rate. The relation of improved diastolic function with verapamil and survival, however, has not been assessed.

In the present study patients with disease-related deaths had reduced peak filling rate and increased relative filling volume by peak filling rate. Although stepwise discriminant analysis revealed these two indexes to be predictors for disease-related death, the overall positive predictive value of the analysis was low (25%). Furthermore, when the analysis included established risk factors, the addition of radionuclide measurements did not improve overall predictability. Reduced peak filling rate was a predictor of sudden death in a retrospective angiographic study, although the overall positive predictive value of the analysis remained low (32%). This did

improve to 43% with inclusion of other clinical/prognostic features. 15 The greater predictive value of angiographic indexes of systolic and diastolic function may in part be due to the longer follow-up (7 years vs 3 years in

the present radionuclide study).

The annual mortality from sudden death is 2 to 4% in adults and approximately 6% in children. 1,2 The cause of sudden death is rarely established, although many mechanisms have been postulated, including autonomic, ischemic and arrhythmia-related changes in diastolic function.<sup>2,3,26</sup> The annual mortality from sudden death in this consecutive patient population of 139 adults, 16 adolescents and 6 children was 1.7%. The small number of sudden deaths (8) limited the power of the analysis and thus the definition of patients with demonstrated electrical instability was broadened to include the 32 survivors with nonsustained ventricular tachycardia during 48-hour ambulatory electrocardiography. The subset with this arrhythmia is known to be at increased risk from sudden death with an annual mortality of approximately 7%.27,28 Patients with electrical instability as defined showed no significant differences in diastolic indexes when compared to survivors without demonstrated electrical instability. The fact that the results were similar when patients with ventricular tachycardia who were receiving amiodarone were either excluded or switched from the survival group to the electrically unstable group does not suggest an important confounding effect of amiodarone by either alteration of diastolic function or prognosis. This is consistent with the observation that long-term administration of amiodarone in patients with HC does not influence radionuclide systolic or diastolic indexes.29

A small proportion of patients with HC experience progressive symptoms and hemodynamic deterioration.<sup>2,3</sup> Not surprisingly, radionuclide measurements were useful in demonstrating significant impairment of both systolic and diastolic function in patients who died from cardiac failure. Radionuclide measurements, however, did not contribute to the prediction of patients who either died suddenly or demonstrated electrical instability with out-of-hospital ventricular fibrillation or nonsustained ventricular tachycardia on 48-hour ambulatory electrocardiography. The low positive predictive value of current cardiologic evaluation for the identification of high-risk patients, particularly the young, underscores a major problem in management of patients with HC.

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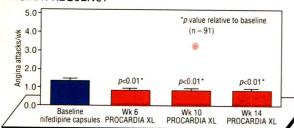
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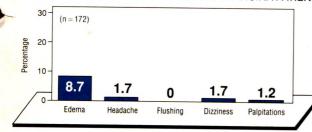




Fourteen-week, open-label, crossover trial to compare the efficacy and dose equivalency of nifedipine capsules (weeks 1 and 2) vs PROCARDIA XL (weeks 3-14) in 98 patients with chronic stable angina who had been on nifedipine capsules at least one month prior to the study. Patients were switched to the nearest equivalent daily dose over the dose range of 30-150 mg/day. Ninety-five patients were crossed over to receive PROCARDIA XL; 91 of these were evaluated for efficacy. The majority remained on beta blockers and/or nitrates throughout the study. (Reported by Vetrovec GW et al., Am.) Med. 1987.¹) Patients were of different races. (Data on file. Medical Department, Pfizer Laboratories, Pfizer Lnc.²)

# ... With a low incidence of vasodilatory side effects<sup>2</sup>

% INCIDENCE OF ADVERSE EXPERIENCES IN ANGINA PATIENTS<sup>2</sup>



Data obtained from multiple controlled trials of PROCARDIA XL (30-150 mg q.d.) in 172 patients with angina. (Data on file. Medical Department, Pfizer Laboratories, Pfizer Inc.<sup>2</sup>)

 The most common side effects are peripheral edema, which is not associated with fluid retention, and headache

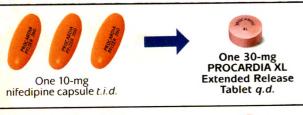
In controlled trials of 776 patients with PROCARDIA XL, edema resulted in discontinuation of therapy in 2.7% of patients  $^2$ 

# ...And no significant changes in heart rate<sup>1</sup>

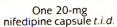
# New, Once-a-Day Procardia XL nifedipine) Extended Release Tablets 30 mg, 60 mg and 90 mg GITS

# <mark>Easy mg-for-mg</mark> switch to convenient, once-daily dosing

Over 90% of angina patients controlled on nifedipine capsules were easily switched to and controlled on PROCARDIA XL Extended Release Tablets at the nearest equivalent total daily dose; others needed dosage adjustment<sup>2</sup>









One 60-mg PROCARDIA XL **Extended Release** Tablet a.d.

# Switch from Nifedipine Capsules to PROCARDIA XL **Extended Release Tablets**

XL Tablets Capsules 30–40 mg/day in divided doses → 30 mg once a day 50-70 mg/day in divided doses  $\rightarrow$  60 mg once a day 80–100 mg/day in divided doses → 90 mg once a day

- Subsequent dosage adjustments may be necessary and should be initiated as clinically warranted
- The total daily dose can be given with multiple tablets once a day, such as two 60-mg PROCARDIA XL Extended Release Tablets to equal 120 mg total daily
- Experience with doses >90 mg in patients with angina is limited; therefore, doses >90 mg should be used with caution and only when clinically warranted

Call 1-800-NOW-RX-XL for additional information on switching to once-a-day PROCARDIA XL Extended Release Tablets.

- References:
   Vetrovec GW, Parker VE, Cole S, et al: Nifedipine gastrointestinal therapeutic system in stable angina pectoris: Results of a multicenter open-label crossover comparison with standard nifedipine. Am J Med 1987:83(suppl 6B):24-29.
   Data on file. Medical Department, Pfizer Laboratories, Pfizer Inc, New York.

Brief Summary

\*\*PROCARDIAL\*\*\* (rifedipine) Extended Release Tablets

FOR OTAI Use

\*\*CONTRAINBICATIONS\*\* Known hypersensitivity reaction to nifedipine.

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\*\*CONTRAINBICATIONS\*\* Known hypersensitivity reaction to most anging patients the hypotension. These responses have usually occurred during mittal thration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant the blockers. Severe hypotension and/or increased fliuld volume requirements have been reported in patients recoving intelligine with the Severe hypotension and/or increased fliuld volume requirements have been reported in patients recoving intelligines with high dose set and any and the contraint of the patients of the p

to surgice.

The following information should be taken into account in those patients who are being treated for hypertension as well as angina. The following information should be taken into account in those patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased requency, duration and/or seventy or angina or acute myocardial infarction on starting intelligene or at the time of dosage increase. The mechanism of this effect is not established.

Beta Blocker Windfrawal: It is important to taper best blockers if possible, rather than stopping them aboughty before beginning related to pine. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased anging, possibly related to interested persistivity. It catechologismies. Intiation of intelligent relatement will not prevent this occurrence and on occasion has been

Bela Blocker Withdrawa! It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning nifedinine. Patients recently withdrawa from beta blockers may develop as withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of infedipine treatment will not prevent this occurrence and on occasion has been reported to increased sincers, reading, patients usually receiving a beta blocker, have developed heart failure after beginning nifedipine. Patients with sight acritic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to do essess benefit to those patients, owing to their tixed impleades to flow across the aortic valve.

PRECAUTIONS: General—Hypotension: Because nifedipine decreases perspheral vascular resistance, careful monitoring of blood pressure different with a production of the production of the set of the production of the productio

2. Data on file. Medical Department, Pfizer Laboratories, Pfizer Inc, New York.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Nitedipine was administered orally to rats, for two years and was not shown to be carcinogenic. When given to rats prior to mating, nitedipine caused reduced tertility at a dose approximately 30 times the maximum recommended human dose. In vivo mutagenicity studies were negative.

Pfregnancy: Pergnancy Category. C. Nitedipine has been shown to be teratogenic in rats when given in doses 30 times the maximum recommended human dose. Mitedipine was embryotoxic (increased fatal resorptions, decreased fetal weight, increased sturted forms increased fetal deaths, decreased enonatal survival in rats, mose a mart arothers of the maximum recommended human dose. Programment monkeys, doses 23 and twice the maximum recommended human dose resorded choration with in rats, doses three times maximum recommended human dose resorded choration with in rats, doses three times maximum recommended human dose resorded choration with rats, doses three times maximum recommended human dose resorded choration with rats, doses three times maximum recommended human dose resorded choration with rats, doses three times maximum recommended human dose resorded choration with rats. A programment of the recommended human dose resorded choration with rats of the recommended human dose resorded choration with rats of the recommended human dose resorded choration with rats of the recommended human dose resorded choration with recommended human dose resorded choration with recommended human dose resorded choration with rats of the recommended human dose resorded hu

More detailed professional information available on request.



# Anti-Beta-Receptor Antibodies in Human Dilated Cardiomyopathy and Correlation with HLA-DR Antigens

Constantinos J. Limas, MD, Catherine Limas, MD, Spencer H. Kubo, MD, and Maria Teresa Olivari, MD

The mechanisms responsible for the decline in the density of  $\beta$ -adrenoceptors in the failing myocardium have not been adequately defined. It is a possibility that the nature of the process leading to heart failure may determine, in large part, the pathogenesis of this decline. Sera of some patients with dilated cardiomyopathy contain antibodies directed against the  $\beta$ -adrenoceptor, as judged by ligand binding inhibition, immunoprecipitation and immunoblotting assays. Because deranged immune function is thought to play a role in dilated cardiomyopathy, immunogenetic markers of the propensity to develop anti- $\beta$ -receptor antibodies were sought. The prevalence of HLA-DR4 was significantly higher in dilated cardiomyopathy patients (40 vs 24% in 511 normal subjects,  $p_c < 0.001$ ). In contrast, no association was found between HLA phenotypes and alcoholic cardiomyopathy. Furthermore, 72% (13 of 18) of the HLA-DR4 dilated cardiomyopathy patients had anti-β-receptor antibodies compared to 22% (7 of 33) HLA-DR4-negative patients; in the latter, presence of antibody was linked to the HLA-DR1 phenotype. Conversely, 67% (15 of 23) of the antibody-positive patients were typed as HLA-DR4 compared to only 10% of the antibody-negative patients. Interestingly, none of the 23 antibody-positive patients were typed as HLA-DR3 while 37% of the antibody-negative did. Only 25% of alcoholic cardiomyopathy patients had anti-β-receptor antibodies and no preponderant **HLA** association could be demonstrated. These results suggest that the presence of anti-β-receptor antibodies in patients with idiopathic dilated cardiomyopathy may be under the control of the major histocompatibility locus.

(Am J Cardiol 1990;65:483-487)

Patients with dilated cardiomyopathy and heart failure have an impaired inotropic response to  $\beta$ -agonists that appears to be accounted for by a lower density of membrane-bound  $\beta$ -receptors (in particular,  $\beta_1$ -adrenoceptors) and decreased isoproterenol-sensitive adenylate cyclase activity. These biochemical defects may limit not only the inotropic reserve of the myocardium, but, also, the usefulness of  $\beta$ -agonists as therapeutic agents. Despite the functional implications of  $\beta$ -adrenergic pathway defects in heart failure, their pathogenesis remains largely speculative.

Recently, we observed that a substantial proportion of patients with dilated cardiomyopathy have autoantibodies directed against the  $\beta$ -adrenergic receptor, as judged by ligand binding inhibition and immunoprecipitation assays. These serum antibodies show preference for the  $\beta_1$ -adrenoceptor, are inactive against cardiac  $\alpha_1$ -receptors and can modify the activity of isoproterenolsensitive adenylate cyclase. Their prevalence and titers are significantly higher in dilated cardiomyopathy compared to patients with ischemic/valvular heart disease or normal control subjects. It is likely, therefore, that autoantibodies play a role in mediating  $\beta$ -receptor abnormalities in this disease entity.

The presence of autoantibodies in dilated cardiomyopathy is not totally unexpected because there is already a substantial body of evidence implicating altered cellular and humoral immunity in the initiation or progression of this disease.<sup>6–9</sup> Since only a subset of cardiomyopathy patients have detectable antireceptor antibodies, it was of considerable interest to examine whether their presence was related to immunogenetic factors determining susceptibility to dilated cardiomyopathy.

# **METHODS**

The frequency-distribution of HLA antigens was compared in 100 patients with dilated cardiomyopathy (HLA-A, -B, -C in 100 and -DR in 97 patients) and a normal hospital population. In addition, the presence of anti-β-receptor antibodies was evaluated in the last consecutive 41 of the 100 patients with dilated cardiomyopathy. Patients with diseases known to be associated with particular HLA phenotypes were specifically excluded from consideration. This included 1 patient with a history of Graves' disease, 2 patients with diabetes mellitus and 1 patient with ankylosing spondylitis. For comparison, the distribution of HLA antigens and antireceptor antibodies was examined in 16 cardiomyopathy patients with a history of habitual excessive ethanol intake (alco-

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**TABLE I** Distribution of Class I HLA Antigens in Normal Subjects (n = 617), Patients with Idiopathic Dilated Cardiomyopathy (n = 100) and Patients with Alcoholic Cardiomyopathy (n = 16)

	HLA-A			HLA-B				HLA-C			
	IDC (%)	AC (%)	N (%)		IDC (%)	AC (%)	N (%)		IDC (%)	AC (%)	N (%)
A1	37.4	31.2	27.4	B7	23.2	12.5	24.8	Cw1	3.1	6.2	7.5
A2	55.5	50.0	49.3	B8	20.2	12.5	19.6	Cw2	7.1	6.2	9.7
A3	28.3	31.2	25.0	B13	7.1	_	3.9	Cw3	19.2	18.7	20.1
A11	9.1	_	11.5	B14	6.1	6.2	7.9	Cw4	13.1	12.5	22.1
Aw24	15.1	12.5	19.4	B27	11.1	12.5	7.6	Cw5	7.1	6.2	11.7
A28	10.1	6.2	8.3	Bw35	7.1	18.7	16.4				
Aw30	9.1	12.5	4.5	Bw39	3.3	12.5	4.2				
Aw32	5.1	_	7.8	Bw44	3.3	25.0	23.2				
				Bw51	8.1	12.5	9.9				
				Bw62	16.2	12.5	10.9				

holic cardiomyopathy). The dilated cardiomyopathy patients were being evaluated as candidates for cardiac transplantation or were participating in the heart failure study program at the University of Minnesota, and had been classified as New York Heart Association class II to IV. They were treated with a combination of diuretics, digoxin and vasodilators.

Lymphocytes for HLA antigen typing were isolated from 20 to 30 ml of heparinized blood using Ficoll-Hypaque density gradient centrifugation, as previously described. 10 Purified B lymphocytes for HLA-DR typing were prepared by the method of Danilovs et al.11 HLA-A, -B and -C antigens were assayed using lymphocyte suspensions with the microcytotoxicity method, while HLA-DR typing was performed in microlymphocytotoxicity assays with prolonged incubation times using isolated B lymphocytes.<sup>12</sup> The statistical evaluation of

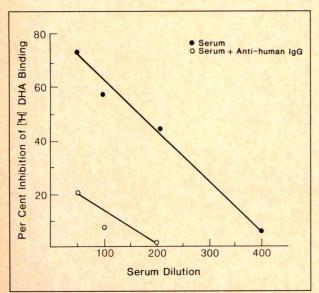


FIGURE 1. A representative ligand-binding inhibition curve. Rat cardiac membranes were incubated with serial dilutions of serum of a patient with idiopathic dilated cardiomyopathy in the presence ( $\odot$ ) or absence ( $\bullet$ ) of 200  $\mu \mathrm{g/ml}$  antihuman immunoglobulin G, for 60 minutes at 30°C before determining (3H) dihydroalprenolol binding (see text). The results refer to (3H) DHA binding to control membranes (incubated in the absence of serum).

the results followed the method of Svejgaard et al. 13 Chi-square 2 × 2 contingency tables were used for comparisons between patient and control groups. Associations involving small numbers were tested with Fisher's exact test. P values were corrected for the number of antigens tested and associations were considered significant if p < 0.05.

The influence of immunogenetic factors in determining the presence of  $\beta$ -receptor antibodies was examined in 50 consecutive patients with idiopathic dilated cardiomyopathy. Those ranged in age from 21 to 76 years (mean 53), and the duration of symptoms was  $3.2 \pm 0.9$ years. Eight were women (19.5%). All had advanced cardiac disease as evidenced by a low ejection fraction  $(20.5 \pm 2\%)$ , high capillary wedge pressure  $(25.2 \pm 3.8)$ mm Hg) and low cardiac index (2.2  $\pm$  0.3 liters/min/ m<sup>2</sup>). All had undergone complete diagnostic work-up, including cardiac catheterization and coronary angiography, and 80% had endomyocardial biopsies.

The presence of autoantibodies against the  $\beta$ -receptor was assessed using the ligand binding inhibition assay as previously described.<sup>5</sup> Rat cardiac membranes were prepared by homogenizing minced ventricular tissues in 5 volumes of cold 50 mM Tris-HCl - 5 mM EDTA, pH 7.5, with a Polytron PT-20 homogenizer at 10 minutes and the supernatants were passed through gauze before centrifugation at 40,000 × g for 15 min at 4°C. The resultant pellet was washed twice and used as the membrane fraction.

For the (3H) dihydroalprenolol (DHA) binding inhibition assay, 100 µl of serum (1:50 to 1:400 final dilution) or buffer was preincubated with 250 µl of the membrane suspension (0.1 to 0.2 mg protein determined by the method of Lowry et al14) in 50 mM Tris- $HCl (pH 7.5) - 5 \text{ mM MgCl}_2 - 0.1 \text{ mM phenylmeth-}$ ylsulfonylfluoride – 5  $\mu$ g/ml leupeptin – 7  $\mu$ g/ml pepstatin for 60 minutes at 30° with dihydroalprenolol (New England Nuclear Co., specific activity 105 Ci/ mmol) and continued to 15 minutes. It was terminated by filtration through Whatman GF/C filters, as previously described.<sup>5</sup> Nonspecific binding was determined in the presence of 1  $\mu$ M propranolol. The number of  $\beta$ receptors was determined from Scatchard plots<sup>15</sup> of the binding data. Immunoblotting of cardiac  $\beta$ -adrenoceptors on rat cardiac membranes was carried out as previously described. 16

#### **RESULTS**

A representative ligand binding inhibition curve is shown in Figure 1. There is a quantitative relation between serum dilution and the extent of (3H) DHA binding to cardiac membranes. Addition of antihuman immunoglobulin G prevented ligand binding inhibition in accordance with the previous observation5 that such inhibition can be induced by immunoglobulin G from cardiomyopathy patient sera. Addition of antihuman immunoglobulin G in the ligand binding assay was by itself ineffective in the absence of patient serum. Cardiomyopathic sera identify 2 polypeptide chains of apparent Mr 67-65 kDa in accordance with previous reports using photo-affinity labeling of canine myocardial β-receptors. 17

In an effort to define immunogenetic influences on the susceptibility of dilated cardiomyopathy, we compared the distribution of HLA class I and II antigens in cardiomyopathy patients (both idiopathic dilated and alcoholic) and normal control subjects. The results, listed in Tables I and II, show that, although HLA-A, -B and -C antigen distribution does not differ between patients with cardiomyopathy and normal subjects, the frequency of HLA-DR4 was significantly higher in the idiopathic dilated cardiomyopathy patients (40 vs 24%, p <0.001). This corresponds to a relative risk factor of 2.24 and an etiologic factor of 0.24. In contrast, the distribution of HLA phenotypes in the alcoholic cardiomyopathy group did not differ from normal subjects.

In view of these findings, we examined whether the distribution of HLA-DR antigens differed in 50 consecutive antireceptor antibody-positive and antibody-negative dilated cardiomyopathy patients, and the results are shown in Figure 2. Two striking differences were noted between the 2 subgroups. First, none of the 23 antibodypositive patients typed as HLA-DR3 while 10 of the 27 antibody-negative patients (37 vs 20% in normal subjects) did. Second, 15 of the 23 antibody-positive pa-

**TABLE II** Distribution of HLA-DR Antigens in Normal Subjects (n = 511), Patients with Idiopathic Dilated Cardiomyopathy (n = 97) and Patients with Alcoholic Cardiomyopathy (n = 16)

HLA-DR Type	IDC (%)	AC (%)	N (%)
DR1	17.5	12.5	20.0
DR2	24.7	25.0	31.5
DR3	30.9	25.0	23.1
DR4	40.2	25.0	24.0*
DR5	19.6	31.0	18.4
DRw6	19.6	25.0	20.0
DR7	17.5	12.5	22.5
DRw8	5.1	6.0	3.4

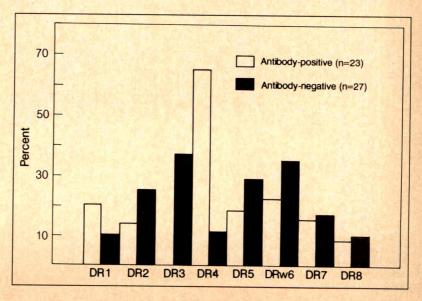
tients (67%) typed as HLA-DR4 compared to only 10% of the antibody-negative patients (3 of 27) (p <0.001). None of the other HLA-DR antigens tested was influenced by the presence of the antibodies.

When the presence of antibodies (ligand binding inhibition at a 100-fold serum dilution) was compared in HLA-DR4 (+) and DR4 (-) dilated cardiomyopathy patients, a significant difference also emerged (Figure 3). Thirteen of the 18 HLA-DR4 (+) patients (72%) had ≥20% inhibition of (3H) DHA binding to cardiac membranes compared to 7 of the 33 HLA-DR4 (-) patients (22%). Furthermore, 4 of the 6 HLA-DR4 (-), DR1 (+) patients (67%) were antibody-positive compared to 12% (3/27) HLA-DR4 (-), DR1 (-) patients. Four of the 16 patients with alcoholic cardiomyopathy (25%) had demonstrable anti-β-receptor antibodies (32.6 ± 5% inhibition of (3H) DHA binding at 1:100 serum dilution). No HLA-DR preponderance was evident in antibody-positive patients; only 1 typed as HLA-DR4 and none as HLA-DR1.

#### DISCUSSION

We have recently reported that sera from dilated cardiomyopathy patients can inhibit ligand binding to cardiac  $\beta$ - (but not  $\alpha_1$ -) adrenoceptors.<sup>5</sup> That this effect

FIGURE 2. Distribution of HLA-DR antigens in 50 idiopathic dilated cardiomyopathy patients, with (n = 23) or without (n =27) evidence of serum anti-β-receptor antibodies by the ligand binding inhibition assay. Numbers in parentheses represent number of patients typing for the particular HLA-DR molecule.



is antibody-mediated is supported by the suppression of the ligand-binding inhibition by antihuman immunoglobulin G and the fact that immunoglobulin G from cardiomyopathy sera also inhibits (3H) DHA binding to cardiac membranes. In addition, such sera can immunoprecipitate the  $\beta$ -receptor and label it in sodium dodecyl sulfate polyacrylamide gels of cardiac membranes. Low titers of anti- $\beta$ -receptor antibodies are present in a small percentage of patients with ischemic or valvular heart disease or even in normal subjects, an observation that has been reported for other known or presumed autoantibodies.18 It would appear that, in dilated cardiomyopathy, this process is amplified so that both the percentage of antibody-positive patients and the antibody titer are higher.

The presence of antiheart antibodies was suggested initially by the demonstration of immunoglobulin binding to cardiomyopathic hearts. 7,8 These findings involved a small number of observations and failed to identify the cellular targets of the presumed autoantibodies and their relation to the evolution of the disease. More recently, antibodies against specific myocardial cell constituents have been identified. These include antibodies against the mitochondrial ATP-ADP carrier, which have also been shown to affect sarcolemmal calcium channels.9 Anti-β-receptor antibodies have previously been reported only in Chagas' cardiomyopathy<sup>19</sup> and are thought to have cytotoxic properties. We do not, as yet, know whether antibodies in idiopathic dilated cardiomyopathy have similar properties.

In view of the postulated immunologic component in the pathogenesis of cardiac damage in many (but not all) patients with dilated cardiomyopathy, we examined whether immunogenetic markers for the disease could be identified. Previous studies in presumed autoimmune disorders have frequently revealed an association of the propensity to disease development with specific HLA phenotypes.<sup>20</sup> In our patient group, the frequency of HLA-DR4 antigen was significantly higher in the dilated cardiomyopathy patients (40 vs 24% in control sub-

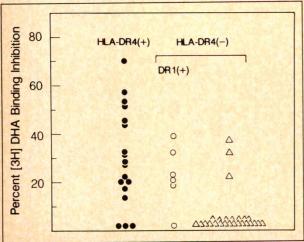


FIGURE 3. Effect of HLA-DR4 status on the (3H) DHA binding inhibition in patients with idiopathic dilated cardiomyopathy. Assays were carried out with a 100-fold serum dilution (see

jects); a similar distribution was recently reported by Komajda et al.<sup>21</sup> In both studies, there was no difference in the frequency of class I HLA antigens. This contrasts with the increase in B27 and decrease in HLA-DRw6 reported by Anderson et al22 in a much smaller series of patients with cardiomyopathy. At least part of the difference may be the inclusion in that series of patients with noncardiac diseases known to show HLA associations.

The nature of the association has not been elucidated by these studies. It may be simply the reflection of a linkage between the HLA locus and an unidentified disease susceptibility gene. Because class II antigens are not normally expressed in the myocardium, the crucial step in the process may be the presentation of self-antigen (e.g.,  $\beta$ -receptor) by abnormally expressed class II molecules. Such expression can be induced by  $\alpha$ -interferon released in response to viral infections.<sup>22</sup> There has been longstanding interest in the possibility, supported by experimental and clinical evidence, that viruses play a role in the pathogenesis of at least some cases of dilated cardiomyopathy.<sup>23</sup> Induction of HLA class II molecules in the myocardium during viral infections may be one of the mechanisms triggering autoimmunity in dilated cardiomyopathy. The other possibility is that autoantibodies represent antiidiotype responses to antiviral antibodies.<sup>24</sup> These mechanisms are still too speculative to warrant extensive discussion, but deserve fur-

ther experimental scrutiny.

The fact that the association between HLA-DR4 and dilated cardiomyopathy is rather modest may be a consequence of the heterogeneity of this disease. It is likely, therefore, that this association might be stronger with a subset of patients, perhaps those with a strong immune component. In fact, 67% of the antibody-positive cardiomyopathy patients typed as HLA-DR4 compared to 10% of the antibody-negative—a near 7-fold difference. Conversely, 81% of the HLA-DR4 patients had antireceptor antibodies defined as ≥20% (3H) DHA binding inhibition at 1:100 serum dilution, compared to 28% of the DR1 (-) patients. The dependence of antireceptor antibodies on HLA-DR phenotype may be even higher than these numbers indicate if we take into consideration the preponderance of HLA-DR1 in the antibody-positive, DR4 (-) patients. This preponderance may provide a clue to the dependence on class II molecules because there is a strong homology between the DR1-β chain and the Dw14 subtype of DR4.25

It is possible that the true association of antireceptor antibodies is with this subtype, a possibility we are actively exploring. It is not known at present whether the linkage between HLA-DR4 (or DR4 subtypes) and the presence of anti-β-receptor antibodies is valid only within the context of dilated cardiomyopathy or would also hold true for cardiac disease of other etiology. Our initial experience with ischemic heart disease patients supports the first alternative; i.e., that the relation holds true primarily for dilated cardiomyopathy patients. Since the prevalence of antireceptor antibodies in ischemic heart disease is low, however, a considerably

expanded patient series will be needed to settle the issue. Similarly, the data on alcoholic cardiomyopathy reported here do not support an association with a particular HLA-DR subtype.

Acknowledgment: The authors wish to thank Dr. F. Bach for many helpful discussions and Dr. A.D. Strosberg for providing the antireceptor antibody (BRK-2).

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#### **Bradycardia-Mediated Tachyarrhythmias** in Congenital Heart Disease and Responses to Chronic Pacing at Physiologic Rates

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The coexistence of bradycardia and a tachyarrhythmia may preclude effective pharmacologic treatment of 1 arrhythmia without paradoxic aggravation of the other. This study evaluated the potential relation between the 2 types of arrhythmias and the effect of conventional modes and rates of pacing for bradycardia on the frequency of the associated tachyarrhythmias. Twenty-one young patients, aged 2 to 19 (mean 11) years with congenital heart disease and a tachyarrhythmia occurring in the setting of chronic bradycardia were studied.

The effects of pacing were evaluated by comparison of the number of episodes of clinical tachycardia during the 12-month intervals before and after pacemaker implantation. During these intervals, antiarrhythmic drug therapy was not altered. Patients were analyzed as independent groups, based on the type of tachyarrhythmia: supraventricular (n = 5), atrial flutter (n = 9) and ventricular (n = 7). The modes of chronic pacing were AAI (n = 4), DDD (n = 6) and VVI (n = 11).

The prevention of bradycardia by pacing was associated with a significant decrease in the frequency of supraventricular (p = 0.008) and ventricular (p = 0.02) tachyarrhythmias. However, the frequency of atrial flutter was not altered. Prevention of tachycardia was more frequently associated with the AAI and DDD modes of pacing compared to VVI (p = 0.08). Pacing represents an effective therapy for certain tachyarrhythmias associated with chronic bradycardia, although critical modes may be required.

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spectrum of tachyarrhythmias has been recognized in patients with chronic bradycardia. These tachyarrhythmias, based on reentry, abnormal automaticity or perhaps triggered activity, may require a substrate of bradycardia, and thus have been termed bradycardia-mediated or bradycardia-dependent.1-4 It has been proposed that cardiac pacing may prevent these tachyarrhythmias by elimination of the substrate of bradycardia.5,6 However, few studies have validated this proposal, and recommendations regarding pacemaker implantation and optimal modes of pacing for this problem have not been made.7 Consequently, antitachycardia pacing research has emphasized the development of pacemakers capable of tachycardia termination, as opposed to prevention.8,9

In some children the onset of supraventricular tachycardia (SVT) follows an abrupt slowing of sinus rhythm. 10 Also, patients with congenital heart defects are recognized to be at particular risk for bradycardia after cardiac surgery, with the subsequent development of various tachyarrhythmias.11-13 Whether cardiac pacing for bradycardia would prevent or reduce the frequency of these tachyarrhythmias or allow discontinuation of antiarrhythmic therapy is uncertain. We present the results of electrophysiologic testing and chronic pacing in young patients with bradycardia-mediated tachyarrhythmias in an attempt to define the relation between the 2 disorders, and the efficacy of chronic rate support in prevention of these tachyarrhythmias.

Between 1983 and 1988, 89 patients with congenital heart disease (0.1 to 21 years old) underwent pacemaker implantation for the treatment of bradycardia at our institution. Preceding pacemaker implantation, the interval of known bradycardia in each patient was reviewed to determine if any tachyarrhythmias had also been documented. In patients identified as having both bradycardia and a tachyarrhythmia, the frequency of tachycardia during the 12-month interval before pacing was determined, based on the number of clinical episodes requiring termination, and number of nonsustained episodes of ventricular tachycardia (VT) during 2 to 4 full disclosure 24-hour Holter recordings.

Atrial flutter, SVT and VT were defined by conventional electrocardiographic criteria, with confirmation during electrophysiologic testing. Sustained VT was defined as >15 seconds' duration, and nonsustained VT as 6 beats to 15 seconds.

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**TABLE I** Patient Characteristics and Associated Diagnoses

Anatomy	Surgery	Bradycardia	Tachycardia	Medication	Age (yrs)	Mode	Lead
D-TGA	Mustard	Sinus	I-A reentry	Digoxin	16	AAI	T
PAPVR	Baffle	Sinus	I-A reentry	Digoxin	9	AAI	T
VSD	Closure	Sinus	AVN reentry	Digoxin	2	VVI	E
ASD	Closure	Sinus	I-A reentry	Digoxin	11	AAI	T
DILV		Sinus	Junctional	Digoxin	5	VVI	E
DILV	Septation	AV block	AF PMT	Dig, Quin	19	DDD	T
D-TGA	Mustard	Slow VR	AF	Dig, Beta	6	VVI	E
DILV	B-H; shunt	Slow VR	AF	Dig, Proc	15	VVI	T
D-TGA	Mustard	Slow VR	AF	Dig, Diso	13	VVI	T
D-TGA	Mustard	Sinus	AF 1:1 VR	Dig, Verap	19	VVI	T
DILV	Fontan	Sinus	AF 1:1 VR	Dig, Verap	4	DDD	E
D-TGA	Mustard	Sinus	AF	Dig, Proc	12	VVI	E
MS, AS	MVR	Slow VR	AF	Dig, Quin	12	DDD/VVI	E
DILV	Fontan	Sinus	AF 1:1 VR	Dig, Proc	8	AAI	E
L-TGA	Shunt	AV block	NSVT	Proc, Toc	8	VVI	E
AS, MS	MVR	AV block	NSVT	Beta, DPH	10	VVI	T
Single V	Fontan	AV block	NSVT	Dig, Mex	10	DDD	E
D-TGA	Mustard	Sinus	NSVT	Dig, Beta	2	DDD	E
Normal		AV block	VT	Beta, DPH	3	DDD	E
D-TGA	Mustard	Sinus	VT	DPH, Proc, Toc	17	VVI	T
Long QT	LCTS	Sinus	VT/VF	Beta, DPH	14	DDD	T

AF = atrial flutter; AS = aortic stenosis; ASD = atrial septal defect; AV = atrioventricular; AVN = atrioventricular node; B-H = Bialock-Hanlon; Beta = beta blockade; D-TGA = transposition of the great arteries; Dig = digoxin; DILV = double inlet left ventricle; Diso = disopyramide; DPH = diphenylhydantion; E = epicardial; I-A = intraatrial; L-TGA = 1-transposition of the great arteries; LCTS = lateral cevicothoracic sympathectomy; Mex = mexilettine; MS = mitral stenosis; MVR = mitral valve replacement; NSVT = nonsustained ventricular tachycardia; PAPVR = partial anomalous pulmonary venous return; PMT = pacemaker-mediated tachycardia; Proc = procainamide; Quin = quinidine; T = transvenous; Toc = tocainide; V = ventricule; Verap = verapamil; VF = ventricular fibrillation; VR = ventricular response; VSD = ventricular septal defect.

The relation of bradycardia to the tachyarrhythmia was evaluated by analysis of the mode of onset when documented by Holter monitoring or electrophysiologic study, and by the frequency of tachycardia at differing basal heart rates.

Electrophysiologic testing was performed in each patient before pacing; it consisted of the determination of resting intervals followed by programmed electrical stimulation. Single and double atrial and ventricular extrastimuli were coupled to the intrinsic rhythm, followed by the decremental addition of 1 to 3 extrastimuli to an 8-beat paced drive train of atrial and ventricular pacing.

After pacemaker implantation, patients were evaluated by a uniform protocol of clinical evaluation, pacemaker interrogation and Holter monitoring at 6-month intervals. Recurrence of tachycardia after pacing was defined as an episode requiring termination, or documentation of the tachycardia during Holter monitoring.

**Study design:** The following eligibility criteria applied: a congenital heart defect, symptomatic bradycardia warranting pacemaker implant, tachycardia documentation during the interval when bradycardia was the primary rhythm and follow-up >12 months before and after pacemaker implant.

A self-controlled design was used to evaluate the effects of pacing on the recurrence of tachycardia. 14 The number of tachycardia episodes per patient requiring termination or the frequency of nonsustained VT during Holter recordings were compared for the 12 month intervals before and after pacemaker implant. Patients were evaluated as independent groups, based on the type of tachycardia: SVT, atrial flutter and VT. The mode of pacing was also evaluated as an independent variable for each type of tachyarrhythmia.

**Criteria for pacemaker implantation:** All patients had either chronic bradycardia associated with symptoms of syncope or congestive heart failure, or advanced atrioventricular block as the primary indications for pacing. The requirement for antiarrhythmic drugs other than digitalis in the presence of bradycardia was a secondary indication for pacing.<sup>15</sup>

Critical rate determination: After pacemaker implant, patients were paced at rates of 80 to 90 beats/min for the first 24 hours. If no ectopy other than isolated premature beats occurred, the basal pacing rate was reduced to 75 to 80 beats/min for the next 24 hours, with final reduction to 72 beats/min, if this rate was judged to be age appropriate and not associated with hemodynamic compromise. Patients were discharged at the lowest basal pacing rate that prevented complex ventricular ectopy or atrial tachycardia.

Follow-up: Any antiarrhythmic medication used on a long-term basis before pacing was continued after pacing, with plasma concentrations maintained within accepted laboratory ranges. An additional antiarrhythmic drug was initiated only if there were ≥2 recurrences of tachycardia during the initial 12-month interval after pacing. Complete elimination of any recurrence of tachycardia without any additional antiarrhythmic therapy was defined as tachycardia prevention. The recurrence of sustained or symptomatic tachycardia in the presence of a normally functioning pacemaker was defined as failure of tachycardia prevention. Recurrence of tachycardia due to pacemaker malfunction was not considered to represent failure, if complete prevention had been present during normal function of the pacemaker. Persistence of <6 premature ventricular contractions/hour or couplets was not considered failure.

**Statistical analysis:** Crossover analysis was performed using the paired t test, and comparison between variables distributed into categories was made using Fisher's exact test. Statistical significance was inferred at a p <0.05.

#### RESULTS

Twenty-one patients (12 males, 9 females) fulfilled entry criteria. The mean age was 11 years at time of pacemaker implant. Patient characteristics and associated diagnoses are summarized in Table I. Of the 21 patients, 19 had surgical palliation or correction of congenital heart disease before the onset of arrhythmia.

Etiologies of bradycardia: Bradycardia was due to sinus node dysfunction in 12, atrial flutter with a slow ventricular response in 4 or advanced second- or third-degree atrioventricular block in 5 patients. Ten of the 12 cases of sinus node dysfunction were associated with surgery involving the right atrium. Progressive atrioventricular block occurred in 3 of 5 cases, with onset of the conduction disturbance from 1 to 3 years after surgery. Two of these patients presented in VT, with atrioventricular block recognized only after the termination of tachycardia.

Tachyarrhythmia characteristics: The electrocardiographic diagnoses of the tachyarrhythmias were SVT in 5 patients, atrial flutter in 9, sustained VT in 3 and nonsustained VT in 4. Each tachycardia was documented by electrocardiography, including the spontaneous onset of tachycardia in 7 patients. There was no correlation between the interval after surgery or the duration of bradycardia and type of tachyarrhythmia.

**Supraventricular tachycardia:** Five patients had SVT, each associated with sinus bradycardia. Spontaneous onset of SVT was recorded in 4 patients, initiated by a premature atrial depolarization during sinus or junctional bradycardia. At electrophysiology study, the mechanisms of intraatrial (n = 3) and atrioventricular node reentry (n = 1) were defined. SVT was not inducible in 1 patient with junctional tachycardia.

Each patient was treated with digoxin before pacing, either for control of tachycardia or inotropic support. During the 12-month interval before pacemaker implant, an average of  $3.2 \pm 0.8$  episodes of SVT per patient required termination. Syncope associated with bradycardia, or the requirement for aggressive antiarrhythmic therapy in the presence of severe bradycardia, was the final indications for pacing.

During the initial 12-month interval after pacing, only 2 episodes of SVT occurred, both in the patient with AV node reentry tachycardia, who required initiation of verapamil therapy (p = 0.008, 95% confidence

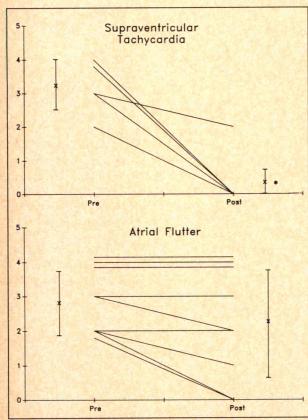


FIGURE 1. The relative frequencies of supraventricular tachycardia (top) and atrial flutter (bottom) before and after pacing. Individual lines refer to the number of episodes of tachycardia per patient, with group means and standard deviation at the sides. The mean number of episodes of supraventricular tachycardia per patient decreased from 3.2 to 0.4 events per year. \*p <0.05. No significant change in the frequency of atrial flutter was observed.

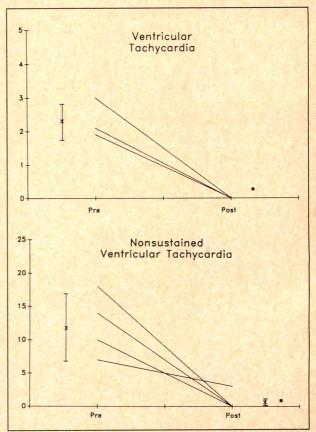


FIGURE 2. The relative frequencies of ventricular tachycardia before and after pacing. No clinical episodes of sustained ventricular tachycardia occurred during the initial 12-month interval after pacing. \*p <0.05. Three of the 4 patients with nonsustained ventricular tachycardia had no recurrences during serial Holter monitoring, and the mean number of episodes was reduced from 12.2  $\pm$  8 to 0.75  $\pm$  0.5 per patient.

intervals  $2.8 \pm 2$ ) (Figure 1). During a total mean follow-up of 27 months, only 1 late recurrence of SVT has been recognized, associated with the discontinuation of

digoxin 2 years after pacemaker implant.

Atrial flutter: Of the 9 patients with atrial flutter, 7 had severe sinus or junctional bradycardia after termination of atrial flutter. Four patients had recurrent asystolic pauses >3 seconds during atrial flutter due to atrioventricular block. Exercise or stress during atrial flutter was accompanied by a 1:1 ventricular response in 3 patients, and a fixed 2:1 response in the others. Three patients had chronic, recurrent atrial flutter, defined as 4 events/year for this study.

This group had an average of 2.8 (± 0.9) episodes of atrial flutter terminated the year before pacing. At electrophysiology study, a corrected sinus node or junctional escape recovery time >1500 ms was demonstrated in 7 of 9 patients. Although retrograde ventriculoatrial conduction was present in 6 patients, atrial flutter was not induced by programmed ventricular stimulation in any patient. At least 2 antiarrhythmic drugs were tested in each patient before pacing. Pacemaker therapy was considered only after repeated episodes of atrial flutter had occurred and pharmacologic trials had proven ineffective or worsened bradycardia.

The overall frequency of atrial flutter was not significantly altered by cardiac pacing (Figure 1). Although there were no early recurrences of atrial flutter in the 3 patients paced in the DDD mode, 1 patient developed pacemaker-mediated tachycardia and another had atrial lead failure, with the loss of atrial stimulation associated with recurrence of atrial flutter. Of 5 patients paced in the VVI mode, 4 had recurrent atrial flutter. Overall, only 2 of 9 patients were free of tachycardia during the first year after pacemaker implant. Three patients with recurrences of atrial flutter after pacing have been successfully treated with amiodarone.

Ventricular tachycardia: Of the 3 patients who developed sustained VT, 2 had underlying sinus bradycardia and 1 congenital complete heart block. Each had ≥2 episodes of clinical VT during the year before pacemaker implantation. VT was monomorphic and sustained in 2 patients, and polymorphic with syncope in 1. VT was inducible during programmed stimulation in 2 patients. Severe bradycardia during antiarrhythmic drug therapy, and suppression of complex ectopy during temporary pacing, were the final indications for pacing.

During the initial 12-month interval after pacing, there were no recurrences of VT (p = 0.02, 95% confidence intervals 2.3  $\pm$  1.2) (Figure 2). A basal pacing rate  $\geq$ 80 beats/min was required in each patient to suppress complex ventricular ectopy. One patient had late recurrent VT, associated with pacemaker failure due to

exit block 34 months after implant.

Nonsustained ventricular tachycardia: Of the 4 patients with nonsustained VT, 3 had progressive failure of atrioventricular conduction. During monitoring, the onset of polymorphic, nonsustained VT characteristically followed abrupt pauses in the intrinsic ventricular rate. An average of  $12.2 \pm 8$  episodes of nonsustained VT per 24-hour Holter monitoring occurred before pacing. Sustained VT was not inducible by programmed

stimulation in these patients, and spontaneous ventricular ectopy was suppressible with paced drive cycle lengths <750 ms.

Cardiac pacing resulted in complete elimination of nonsustained VT in 3 patients, and a mean of 0.75 episodes per 24-hour Holter monitoring (p = 0.02) (95% confidence intervals 11.5 ± 9.8) (Figure 2). Addition of a class 1a drug was required in 1 patient to suppress tachycardia. Pacing at rates ≥80 beats/min were required to suppress complex ventricular ectopy.

Critical modes and rates of pacing: The 3 modes of pacing used in this study were: AAI (n = 4), DDD (n = 6) and VVI (n = 11). Compared to the VVI mode, fewer patients with AAI or DDD modes of pacing had recurrence of tachycardia (p = 0.08) (Figure 3). Ten patients were paced at 72 beats/min, 8 at 80 beats/min and 3 at 90 beats/min.

#### DISCUSSION

Mechanisms of bradycardia-mediated tachyar-rhythmias: This study supports the tenet that certain tachyarrhythmias require a substrate of bradycardia, either for initiation or perpetuation. 4,7,10 Induction of the clinical tachycardia by programmed stimulation in 15 of 21 patients (71%) in this series would suggest a reentrant basis for most of these tachyarrhythmias. Prior clinical and laboratory studies have shown that prolonged cycle lengths increase the temporal dispersion of refractoriness, which may favor the development of reentry. 17,18

Dispersion of refractoriness, however, does not explain the de novo generation of ectopic beats, which clinically initiate these tachyarrhythmias. During bradycardia, an impulse must interrupt the refractory period to generate the first beat of a tachyarrhythmia. <sup>19</sup> Both increased automaticity and early after-depolariza-

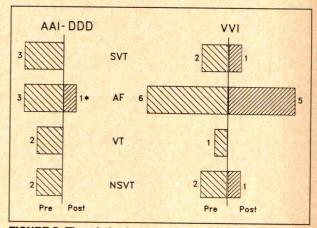


FIGURE 3. The relation between modes of pacing and observed recurrences of tachycardia. The values refer to the number of patients with a specific type of tachycardia, paced either in the AAI-DDD or VVI modes. Of 10 patients paced in the AAI or DDD modes, only 1 had tachycardia after pacing, which was controlled with a physician-activated antitachycardia option. One other patient with DDD pacing had pacemaker-mediated tachycardia (\*). In contrast, 7 of 11 patients with VVI pacing had recurrences of tachycardia, none associated with pacemaker malfunction. AF = atrial flutter; NSVT = nonsustained ventricular tachycardia; SVT = supraventricular tachycardia; VT = ventricular tachycardia.

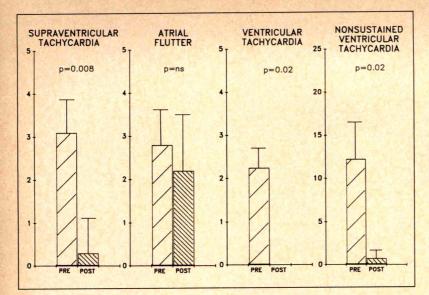


FIGURE 4. The composite results of pacing for the prevention of the bradycardiamediated tachyarrhythmias. The frequencies of supraventricular and ventricular tachyarrhythmias were significantly reduced after pacing. However, similar efficacy was not demonstrated for atrial

tions have been proposed as mechanisms for the premature beats during bradycardia that initiate tachycardia involving a reentry circuit.20,21

Thus, prevention of bradycardia-mediated tachyarrhythmias by pacing may be related to the following consequences of the shortening of electrical diastole, affecting both automaticity and reentry. The first is that reduction in ectopic activity may occur due to prevention of phase 4 depolarization. A similar reduction in early after-depolarizations would be anticipated, given the inverse relation between this type of triggered firing and heart rate.4 The second is that shortening of the intrinsic cycle length reduces the temporal dispersion of refractoriness, which may prevent the development of slow conduction and reentry. The third is that pacing decreases the interval during which a potential reentry circuit may respond to a premature beat. The prevention of bradycardia-mediated tachyarrhythmias by pacing, which may depend on a critical shortening of the period of repolarization, appears similar in effect to the proposed role of pacing in long QT syndrome.22

Efficacy of pacing in the prevention of bradycardiamediated tachyarrhythmias: During the initial 12month interval after pacing, 10 of the 12 patients (83%) with SVT or VT had no recurrence of tachycardia, with no additional antiarrhythmic therapy. Adjunct drug therapy, required in 2 other patients, could not have been initiated before pacing due to concomitant bradycardia. Similar efficacy of pacing for the prevention of bradycardia-mediated tachyarrhythmias, associated with other forms of heart disease, have been reported.23-25 The dependency of tachycardia prevention on rate support was further confirmed by long term follow-up, during which there were 2 late recurrences of tachycardia, both related to pacemaker failure.

In comparison to SVT or VT, pacing was ineffective in the prevention of atrial flutter (Figure 4). This finding is concordant with the Collaborative Study of Atrial Flutter in the Young, which reported that neither the incidence of sudden death nor success of drug therapy differed in patients with or without pacemaker therapy.26 However, functional status and modes of pacing were not specified in this study. Conversely, Gillette et al<sup>27</sup> reported 100 cases of atrial synchronous pacing in children, including an unspecified number with atrial flutter before pacing. During a mean follow-up of 19 months, they<sup>27</sup> reported no recurrence of atrial flutter.

As all patients in this study with atrial flutter had prior surgery, the presence of a fixed reentry circuit, not dependent on bradycardia, may account for the inefficacy of rate support alone in the prevention of this arrhythmia.<sup>28</sup> In the presence of a stable reentrant circuit and bradycardia, AAI or DDD pacing, with automatic or manually activated antitachycardia pacing options, may be preferential.<sup>29</sup> However, data to support this approach are limited.

Critical modes of pacing: Relative efficacy of AAI or DDD pacing in prevention of bradycardia-mediated tachyarrhythmias has been reported.30,31 Based on the limited number of patients in this study and the frequent use of VVI pacing in atrial flutter, firm conclusions are not warranted. Arrhythmia suppression may require a critical activation sequence after a paced impulse to prevent establishment of a reentrant circuit.

Cautious application of pacemaker therapy, with strict attention to the characteristics of electrogram sensing, are required in patients with bradycardia-mediated tachyarrhythmias. Further studies in such patients, to define more precisely the role of cardiac pacing in the suppression of tachyarrhythmias, are indicated.

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## Effect of Beta Adrenoceptors and Thyroid Hormones on Velocity and Acceleration of Peripheral Arterial Flow in Hyperthyroidism

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Brachial artery flow patterns were studied in 10 hyperthyroid and 10 normal subjects. Mean blood velocity and flow were evaluated by pulsed Doppler, and peak systolic acceleration was calculated by computer-assisted digitization of the instantaneous velocity curve. Compared to control subjects, hyperthyroid patients had higher velocity and flow (p <0.01, p <0.02) and higher peak systolic acceleration (p <0.01). In hyperthyroid patients, measurements were repeated after (1) mechanical exclusion of the hand from brachial circulation, (2) short-term  $\beta$ -blocker treatment and (3) inducement of the euthyroid state. Exclusion of the hand reduced velocity and flow (p < 0.001) but did not change peak systolic acceleration. Beta blockade induced disparate changes of velocity and flow but reduced peak systolic acceleration (p <0.05). In the euthyroid state, decreased blood velocity (p <0.01), flow (p <0.02) and acceleration (p <0.02) were observed. A hyperkinetic arterial circulation consisting of an increase in both velocity and acceleration is thus observable in hyperthyroidism. Hand exclusion showed that velocity seems to be influenced by peripheral factors while  $\beta$  blockade suggests that acceleration is dependent of  $\beta_1$  adrenoceptors. Comparison between euthyroidism and hyperthyroidism indicates that both mean blood velocity and peak systolic acceleration are influenced by thyroid hormones.

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The hyperdynamic circulatory state observed during thyrotoxicosis has been well documented at the cardiac level<sup>1-5</sup> but few investigations have concerned the peripheral regional circulation. Blood flow in the limbs is increased in hyperthyroid states, 6-8 but for methodologic reasons the venous occlusion plethysmographic technique previously used neither provides absolute flow values nor permits analysis of the velocity characteristics of flow. 9,10 This study is an original analysis of flow patterns in the brachial artery of hyperthyroid patients. We used an ultrasonic range-gated pulsed Doppler flowmeter, which provides noninvasive measurements of arterial flow in terms of artery caliber, intraarterial blood velocity<sup>9,10</sup> and blood acceleration. We explored the effects of 3 interventions on brachial artery circulation: the mechanical exclusion of blood flow to the hand, which discriminates between skin-related circulation and circulation related to the skeletal muscle, 10 the short-term administration of  $\beta$ -blocking drugs (to investigate the role of  $\beta$  adrenoceptors)<sup>11,12</sup> and the inducement of the euthyroid state (to evaluate the role of thyroid hormones).6-8,13

#### METHODS

Patients: Ten hyperthyroid patients (7 women and 3 men) were examined. Seven had Graves' disease and 3 had nodular toxic goiter. The diagnosis of uncomplicated thyrotoxicosis was assessed on the basis of clinical data and confirmed by hormonal analysis. Ten normal age- and sex-matched subjects, with no history or clinical features of thyroid disorder, were also studied. The hyperthyroid patients had stopped all β-blocker or antithyroid treatment for at least 1 month. We verified, on the basis of case history, physical examination, electrocardiogram, chest radiography and peripheral Doppler measurements, that all the subjects were in sinus rhythm and none had congestive heart failure, valvular or coronary artery disease, arteriosclerosis obliterans of the lower limbs or arterial hypertension. Clinical characteristics of control subjects and patients are listed in Table I. After giving informed consent, the control subjects and hyperthyroid patients were referred to the hemodynamic laboratory, where the noninvasive arterial measurements were carried out after a light lunch.

**Protocol:** The study was performed with the subjects supine in a warm and quiet room. The right arm was supported at the midthoracic level in a controlled environment at  $20 \pm 1^{\circ}$ C with the hand relaxed and opened. After 10 minutes of rest, systemic blood pressure was measured in the left arm as the mean of at

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least 3 measurements, by the standard sphygmomanometric procedure (Table I). Brachial artery circulation was studied by means of a bidimensional pulsed Doppler velocimeter with a frequency of 8 MHz pulsed at 15 kHz. It has 2 important features previously described9: a double transducer probe permitting adjustment of the ultrasonic beam's incident angle at 60 ± 1° to the arterial axis, permitting quantification of blood velocity inside the artery, and a range-gated time system of reception, which made it possible to locate precisely the proximal and the distal walls of the artery, and thus to deduce the internal diameter of the brachial artery and to measure the instantaneous velocity of the whole arterial blood column. The mean blood velocity was obtained by means of electronic integration of the instantaneous blood velocity curve. It was used to calculate mean blood flow in the brachial artery (Q) in accordance with the formula:  $Q = (\pi D^2/4) \cdot VM$  where D is internal diameter and VM is mean blood velocity. Arterial diameter and mean blood velocity were determined at least twice in each patient for each probe with a variability of  $7 \pm 2$  and  $5 \pm 2\%$  (mean  $\pm$  standard error), and were expressed in cm and cm/s, respectively.

Peak systolic blood acceleration was obtained by digitizing the instantaneous blood velocity curve with a Hewlett-Packard 46088A table interfaced with a Hewlett-Packard 217 microcomputer (Figure 1). Before digitizing, each stripchart was calibrated for time (2.5 seconds) and velocity (38 cm/s). The data were analyzed

**TABLE I** Comparison of Morphologic and Clinical Characteristics in Control Subjects and Hyperthyroid Patients

	Control Subjects (n = 10)	Hyperthyroid Patients (n = 10)
Sex: M/F	3/7	3/7
Age (yrs)	$50 \pm 3$	50 ± 3
Weight (kg)	$63 \pm 3$	54 ± 2*
Height (cm)	160 ± 3	162 ± 2
Systolic blood pressure (mm Hg)	119 ± 4	133 ± 4 <sup>†</sup>
Diastolic blood pressure (mm Hg)	75 ± 2	77 ± 3
Heart rate (beats/min)	64 ± 3	101 ± 2‡

Values are mean  $\pm$  1 standard error of the mean. \* p <0.05, † p <0.01, ‡ p <0.001.

with a resolution of 10 ms and with a moving average filter using a 7-point smoothing algorithm to calculate the instantaneous first derivative, that is, the instantaneous blood acceleration (Figure 1). The accuracy of this technique was improved by digitizing the velocity curve at least 3 times before calculation, to reduce intraobserver variability. The computed values of peak systolic acceleration were averaged out for 6 cycles, that is, 3 consecutive cycles for each transducer probe, and were expressed in cm/s<sup>2</sup>. The intraobserver variability was  $1.9 \pm 0.6\%$  (mean  $\pm$  standard error). The interobserver variability was  $2.1 \pm 0.4\%$ .

Hormonal analysis, including fasting serum thyroxin (T<sub>4</sub>) (normal range 60 to 160 nmol/liter), triiodothy-

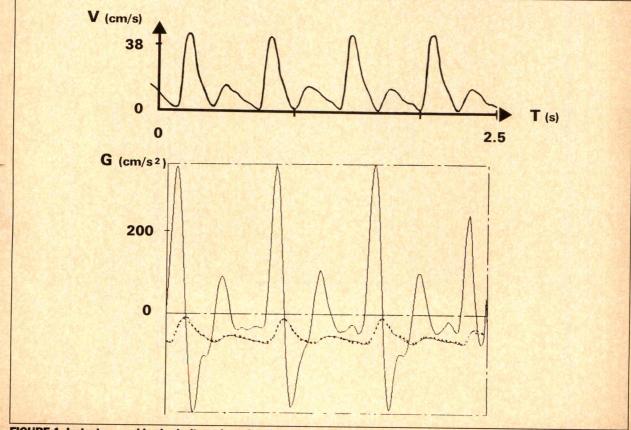


FIGURE 1. Instantaneous blood velocity and acceleration waves in a control subject. *Top* is the blood velocity curve (V) recorded by the Doppler apparatus as a function of time (T). *Bottom*, the digitized velocity curve (*dotted line*) and instantaneous acceleration (*solid line*).

TABLE II Comparison of Brachial Hemodynamics in Control Subjects and Patients

	Control Subjects	Hyperthyroid Patients
Brachial artery diameter (cm)	0.416 ± 0.017	$0.415 \pm 0.024$
Brachial artery blood velocity (cm/s)	$5.5 \pm 0.5$	$11.2 \pm 1.8^{\dagger}$
Brachial artery blood flow (ml/min)	47 ± 7	91 ± 15*
Brachial artery peak systolic acceleration (cm/s²)	354 ± 22	507 ± 36 <sup>†</sup>

\* p <0.02, † p <0.01

ronin (T<sub>3</sub>) (normal range 1 to 3 nmol/liter) and thyrotropin, was determined by radioimmunoassay kits (Behring Institute) at 8 A.M. 14 The free T4 index was obtained by calculating the ratio T<sub>4</sub> (nmol/liter)/moles of T<sub>3</sub> binding capacity (normal range 60 to 160). In all our hyperthyroid patients, serum thyrotropin level was below the detection limit (0.4 µIU/ml) before any treatment, and the response to the intravenous injection of 200 µg thyrotropin releasing hormone (Protireline, Roche) was blunted.14

The hyperthyroid patients underwent 3 successive interventions: exclusion of the hand, short-term  $\beta$  blockade and inducement of a euthyroid state.

Mechanical exclusion of the hand: Brachial artery measurements were repeated with the circulation of the hand arrested by inflating a cuff around the wrist to 250 mm Hg at least 3 minutes before the measurements.10

Short-term beta-blocker treatment: Beta blockers were orally administered by randomly choosing either propranolol (5 patients) or atenolol (5 patients). Brachial artery measurements were repeated after 7 days of  $\beta$ blockade, at a mean daily dosage of 108 ± 27 (± 1 standard deviation) mg for propranolol and 175  $\pm$  48 mg for atenolol. Dosages were adjusted to obtain a heart rate between 75 and 85 beats/min for each patient.

Euthyroid state: After 7 days of β-blocker treatment, the antithyroid drug carbimazole was administered at an initial oral dose of 60 mg, and concomitant β-blocking treatment was progressively stopped. The euthyroid state, as attested by hormone analysis, was studied in 7 patients. It was obtained by carbimazole alone in 4 patients and by associating carbimazole to either subtotal thyroidectomy (1 patient) or radioiodine (2 patients). Brachial artery measurements were repeated both during the euthyroid state and at least 1 month after  $\beta$ -blocking treatment was stopped.

Statistical analysis: Values are mean ± standard error of the mean. For statistical analysis, we used the Wilcoxon ranked-sum and signed-rank 2-tailed tests for 2 samples and matched pairs, respectively. 15 Differences

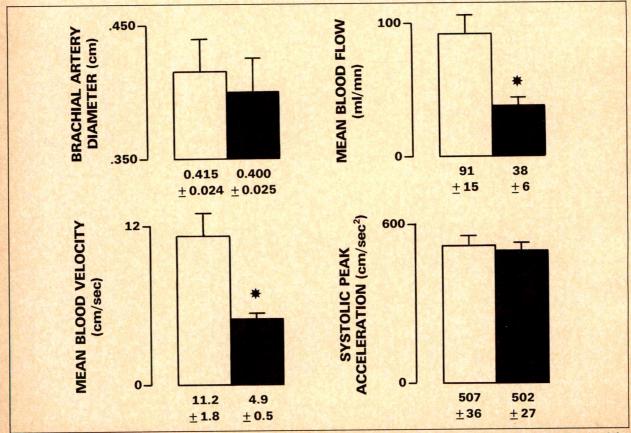


FIGURE 2. Effects of wrist occlusion on brachial circulation in hyperthyroid patients. Values are mean  $\pm$  1 standard error of the mean. Only statistically significant differences are shown. \*p <0.001. White columns indicate before wrist occlusion; black columns indicate after wrist occlusion.

were considered significant at p <0.05. Correlations between parameters were made according to the Spearman correlation.<sup>15</sup>

#### RESULTS

**Basal study:** Tables I and II show that compared to control subjects, hyperthyroid patients had higher systolic blood pressure (p <0.01), higher heart rate (p <0.001), higher brachial artery mean blood velocity (p <0.01) and flow (p <0.02), and higher peak systolic acceleration (p <0.01).

**Exclusion of the hand:** In hyperthyroid patients, wrist occlusion did not significantly modify heart rate, systemic blood pressure, brachial artery diameter and peak systolic acceleration, but significantly reduced brachial artery mean blood velocity (p <0.001) and flow (p <0.001) (Figures 2 and 3).

**Beta blockade:** In hyperthyroid patients, both propranolol and atenolol reduced heart rate ( $102 \pm 3$  vs 77  $\pm$  4 beats/min, p <0.05, and  $101 \pm 3$  vs 78  $\pm$  3 beats/min, p <0.05 before and after propranolol and atenolol, respectively), systolic blood pressure ( $134 \pm 6$  vs  $128 \pm 6$  mm Hg, difference not significant, and  $133 \pm 4$  vs

**TABLE III** Comparison of Hormonal Values Between Baseline Hyperthyroidism and Both Beta-Blocking and Antithyroid Treatment

	Before Treatment (n = 10)	Beta-Blocking Treatment (n = 7)	Euthyroid State (n = 7)
Thyroxin T <sub>4</sub> (nmol/liter)	257 ± 22	285 ± 24	106 ± 13*
Free T <sub>4</sub> index	$349 \pm 48$	$365 \pm 27$	101 ± 13*
Triiodothyronin T <sub>3</sub> (nmol/liter)	$6.10 \pm 0.96$	$6.25 \pm 0.98$	1.66 ± 0.19 <sup>†</sup>

Values are mean  $\pm$  1 standard error of the mean. \* p <0.05, † p <0.01.

118  $\pm$  6 mm Hg, p <0.05 before and after propranolol and atenolol, respectively) and diastolic blood pressure (76  $\pm$  5 vs 71  $\pm$  5 mm Hg, p <0.05, and 78  $\pm$  5 vs 71  $\pm$  4 mm Hg, p <0.05 before and after propranolol and atenolol, respectively). Figure 4 shows that both propranolol and atenolol reduced brachial artery peak systolic acceleration (p <0.05). The decrease in peak systolic acceleration observed after  $\beta$  blockade was not sta-

tistically linked to the decrease in heart rate (r = 0.103,

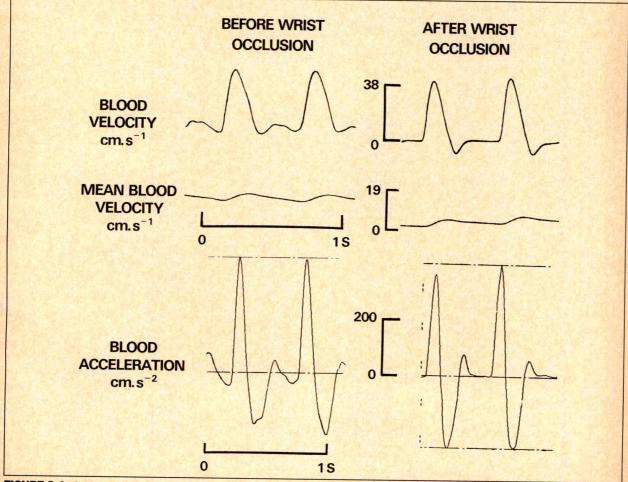


FIGURE 3. Instantaneous (top) and mean (middle) blood velocity, and instantaneous acceleration (bottom) waveforms in the brachial artery of a hyperthyroid patient before (left) and after (right) inflating a cuff around the wrist to 250 mm Hg for at least 3 minutes. The pulsatile components of flow, that is, the peak systolic acceleration and maximal blood velocity, were not modified. Conversely, the increased reflections of velocity wave against the inflated cuff around the wrist shortened the width of the positive part of the instantaneous velocity curve and induced a marked backflow. This resulted in a marked decrease in mean blood velocity.

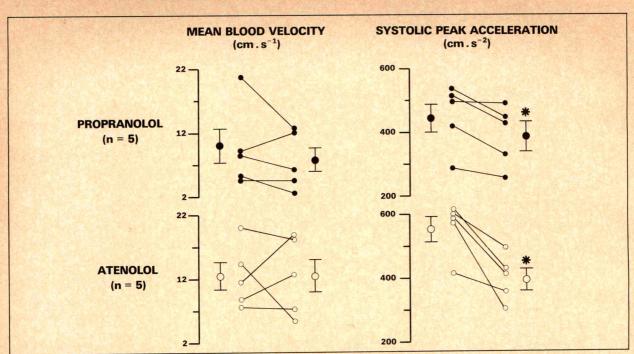


FIGURE 4. Left, individual response of brachial artery mean blood velocity to propranolol and atenolol in hyperthyroid patients. The response was random, with no significant change in mean values. Right, individual response of brachial artery peak systolic acceleration to propranolol and atenolol in hyperthyroid patients. All subjects had a decrease in systolic acceleration that was marked in 9 of 10 patients and only slight in 1. After both drugs, the mean value of peak systolic acceleration significantly decreased. \*p <0.05.

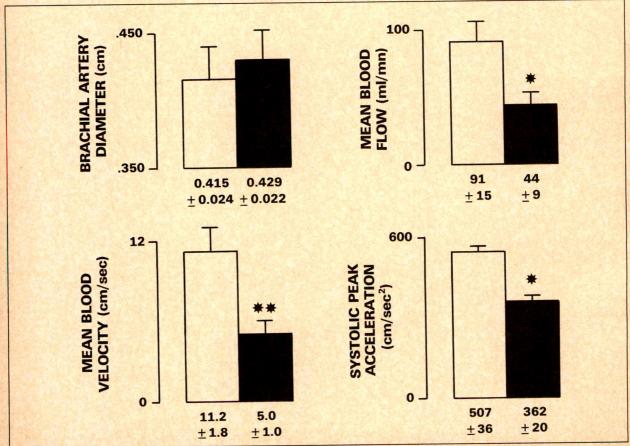


FIGURE 5. Comparison of brachial artery circulation during hyperthyroid and euthyroid states. Values are mean  $\pm$  1 standard error of the mean. Only statistically significant differences are given. \*p <0.02, \*\*p <0.01. White columns indicate hyperthyroid state; black columns indicate euthyroid state.

relation not significant). On the other hand, neither propranolol nor atenolol significantly changed brachial artery diameter (0.394  $\pm$  0.024 vs 0.381  $\pm$  0.028 cm and 0.437  $\pm$  0.022 vs 0.423  $\pm$  0.025 cm before and after propranolol and atenolol, respectively), mean blood velocity (Figure 4) and flow (69  $\pm$  18 vs 57  $\pm$  21 ml/min and 114  $\pm$  20 vs 102  $\pm$  35 ml/min before and after propranolol, respectively). Lastly, neither of these 2  $\beta$  blockers changed the thyroid hormone level (Table III).

**Euthyroid state:** The euthyroid state decreased brachial artery mean blood velocity and flow (p <0.01 and p <0.02, respectively) and peak systolic acceleration (p <0.02) (Figure 5). These 3 parameters did not show statistical difference versus those of control subjects. Heart rate decreased significantly ( $101 \pm 2 \text{ vs } 79 \pm 6 \text{ beats/min, p} <0.01$ ). The decrease in peak systolic acceleration observed with antithyroid therapy was not statistically linked to the decrease in heart rate (r = -0.464, relation not significantly vary ( $133 \pm 4 \text{ vs } 129 \pm 5 \text{ mm Hg}$  and  $77 \pm 3 \text{ vs } 80 \pm 3 \text{ mm Hg}$ , respectively). We also observed a decrease in triiodothyronin (p <0.01), thyroxin (p <0.05) and free  $T_4$  index (p <0.05) (Table III).

#### DISCUSSION

The hyperdynamic state observed during thyrotoxicosis has been poorly documented at the peripheral circulatory level. 6-8,16 Some observations of increased skin and muscle blood flow in the limbs, estimated by means of venous occlusion plethysmography, have been reported in hyperthyroid patients 6-8 but do not provide accurate data regarding flow characteristics 9,10 such as blood velocity and acceleration. In the present study, these latter parameters were investigated in the brachial artery of thyrotoxic patients by using a range-gated pulsed Doppler flowmeter. 9 Our study indicates that both mean blood velocity and flow and peak systolic acceleration are higher in thyrotoxic patients than in control subjects.

During hyperthyroidism, the increase in heart rate and the enhanced inotropic state<sup>1-5,17,18</sup> contribute to a marked acceleration of the rate at which blood is ejected from the ventricle. <sup>19,20</sup> The decreased peripheral arterial resistance of hyperthyroid patients, <sup>1,2,4</sup> which is not entirely explained by variations in peripheral oxygen consumption, <sup>21</sup> may also contribute to increased flow in peripheral circulatory beds. To determine the relative contribution of these central and peripheral mechanisms, 3 successive interventions were performed: mechanical exclusion of the hand, <sup>10</sup> short-term beta-blockade and inducement of a euthyroid state.

Mechanical exclusion of the hand from the brachial circulation for at least 3 minutes decreased mean brachial artery blood velocity and flow but did not modify peak systolic acceleration. Reduction in mean blood velocity may well be due to tissue restriction and increased reflections of velocity wave against the inflated cuff around the wrist. <sup>10</sup> This also suggests that enhanced mean blood velocity in the brachial artery of hyperthy-

roid patients is mediated in part by peripheral local mechanisms in the circulatory bed of the hand. The lack of change in blood acceleration during wrist occlusion suggests that blood acceleration in conduit arteries is less influenced by peripheral resistance factors than by cardiac performance.

This point was recently demonstrated for peak aortic blood acceleration, <sup>22,23</sup> which seems to be a good indicator of the inotropic state of the heart. <sup>24–26</sup> Thus, the enhanced inotropic level <sup>5,17,18</sup> and the acceleration of the rate at which the blood is ejected from the ventricle <sup>19,20</sup> may partly explain the high values of brachial artery peak systolic blood acceleration observed in our study in thyrotoxic patients. However, the nonuniform regional distribution of blood flow in hyperthyroidism <sup>1,8</sup> suggests that the variations in the distribution of cardiac output in systemic circulation may be also involved in increased blood acceleration in the brachial artery.

Several reports have emphasized the role of the  $\beta$ -adrenergic system in cardiovascular manifestations of thyrotoxicosis 11,12,27 but few have studied the peripheral regional circulation. We compared the effect of selective and nonselective short-term beat-blockade on the brachial artery circulation of thyrotoxic patients. Levenson et al 28 previously showed that the increase in mean brachial blood flow observed in borderline hypertension was eliminated by a nonselective  $\beta_1$ -blocking agent but not by a selective one. For ethical reasons, only short-term  $\beta$ -blocker treatment was given, and blood pressure and pulse effects were modest. However, similar significant decreases in heart rate were observed after both propranolol and atenolol and were related to the  $\beta_1$ -adrenergic blocking effect of the drugs.

The significant decrease in peak systolic acceleration obtained both with propranolol and atenolol suggests that  $\beta_1$  adrenoceptors contribute to increased blood acceleration in hyperthyroid patients, and thus corroborates the results of wrist occlusion. However, the fact that the acceleration did not exactly return to control level may suggest that the thyroid hormone acts on the myocardium by 2 different pathways. The first is direct and independent of catecholamines17 and the other is dependent of the effects of catecholamines on the adenylcyclase system. Conversely, the small population size and heterogenous characteristics of the 2 study subgroups make it difficult to draw any conclusions concerning the evolution of mean blood velocity and flow. It must be noted that propranolol and atenolol induced disparate changes of steady blood flow and velocity while they both decreased pulsatile flow in each hyper-

thyroid patient. Our last aim was to investigate whether the normalization of serum thyroid hormone levels was accompanied by a correction of peripheral vascular hyperkinesis, as this was observed for the hyperdynamic cardiac state.  $^{2-4}$  Our findings clearly indicate that, in the euthyroid state as attested by the normalization of thyroid hormones, both brachial artery blood velocity and acceleration decreased significantly toward control values. Thus, while both antithyroid therapy and  $\beta$  blockade reduced heart rate to a similar extent, only antithyroid

therapy completely normalized the brachial hyperkinetic circulation. This suggests that velocity and acceleration of peripheral arterial blood flow are more sensitive indexes of the circulating effects of the thyroid hormones than heart rate.

Finally, the present study suggests that thyroid hormones induce a hyperdynamic state in large peripheral arteries. In circulatory hyperkinesis, this dissociation between increased blood velocity and increased blood acceleration is of interest because it seems to indicate that mean blood velocity relates to peripheral vascular factors while peak systolic blood acceleration is instead related to intrinsic cardiac mechanisms. Thus, noninvasive Doppler measurements of the functional state of a peripheral arterial circulation allow a rapid estimate of the chemical states of thyrotoxic patients before and after antithyroid treatment.

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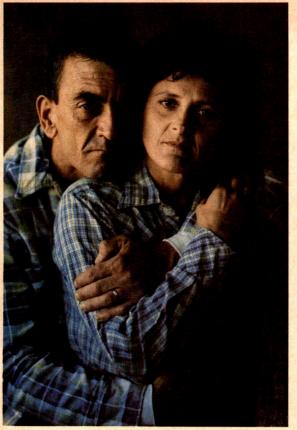
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Concomitant use of heparin anticoagulation may contribute to bleeding. Some hemorrhagic episodes occurred one or more days after the effects of ACTIVASE® had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during ACTIVASE® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including sites of catheter insertion, arterial and venous puncture, cutdown and needle puncture). Intramuscular injections and nonessential handling of the patient should be avoided during treatment with ACTIVASE® venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of ACTIVASE® it is preferable to use an upper extremity vessel accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding. Should serious bleeding (not controllable by local pressure) occur, the infusion of ACTIVASE® and any concomitant heparin should be terminated immediately.

Each patient being considered for therapy with ACTIVASE® should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

In the following conditions, the risks of ACTIVASE® therapy may be increased and should be weighed against the anticipated benefits. Recent (within 10 days) major surgery, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels. \*Cerebrovascular disease.\* Recent (within 10 days) gastrointestinal or genitourinary bleeding. \*Recent (within 10 days) trauma. \*Hypertension: systolic BP≥180 mm Hg and/or diastolic BP≥110 mm Hg.\* High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation. \*Acute pericarditis. \*Subacute bacterial endocarditis. \*Hemostatic defects including those secondary to severe hepatic or renal disease. \*Significant liver dysfunction. \*Pregnancy. \*Diabetic hemorr

analysis. Collection of blood samples in the presence of aprotinin (150-200 units/mL) can to some extent mitigate this phenomenon.

Drug Interactions The interaction of ACTIVASE® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that after platelet function may increase the risk of bleeding if administered prior to, during or after ACTIVASE® therapy.

Use of Anticagualuants Heparin has been administered concomitantly with and following infusions of ACTIVASE® to reduce the risk of rethrombosis. Because either heparin or ACTIVASE® alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites. Pregnancy (Category C) Animal reproduction studies have not been conducted with ACTIVASE® it is also not known whether ACTIVASE® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ACTIVASE® should be given to a pregnant woman only if clearly needed

clearly needed.

Pediatric Use Safety and effectiveness of ACTIVASE® in children has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which evaluated tumorigenicity of ACTIVASE® and effect on tumor metastases in rodents, were negative. Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure and only at the highest concentrations tested.

Nursing Mothers It is not known whether ACTIVASE® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ACTIVASE® is administered to a

nursing woman.

ADVERSE REACTIONS: Bleeding The most frequent adverse reaction associated with ACTIVASE® is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

The following incidence of significant internal bleeding (estimated as>250 cc blood loss) has been reported in studies in over 800 patients treated at all doses.

Total Dose ≤ 100 mg gastrointestinal 4% genitourinary ecchymosis retroperitoneal gingival

The incidence of intracranial bleeding in patients treated with ACTIVASE® Alteplase, recombinant, is as follows:

Dose	Number of Patients	<u>%</u>
100 mg	3272	0.4
150 mg	1779	1.3
1-1.4 mg/kg	237	0.4

These data indicate that a dose of 150 mg of ACTIVASE\* should not be used because it has been associated with an increase in intracranial bleeding.

Recent data indicate that the incidence of stroke in 6 randomized double-blind placebo controlled trialst7 is not significantly different in the ACTIVASE\* treated patients compared to those treated with placebo (37/3161, 12% versus 27/3092, 0.9%, respectively) (p = 0.26).

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, ACTIVASE\* therapy should be discontinued immediately, along with any concomitant therapy with heparin.

Fibrin, which is part of the hemostatic plus formed at needle nuncture sites, will be lived during

therapy with heparin.

Fibrin, which is part of the hemostatic plug formed at needle puncture sites, will be lysed during ACTIVASE\* therapy. Therefore, ACTIVASE\* therapy requires careful attention to potential bleeding sites. 

Allergic Reactions No serious or life-threatening allergic reactions have been reported. Other mild hypersensitivity reactions such as urticaria have been observed occasionally.

Other Adverse Reactions Other adverse reactions have been reported, principally nausea and/or vomiting, hypotension, and fever. These reactions are frequent sequelae of MI and may or may not be attributable to ACTIVASE\* therapy.

DOSAGE AND ADMINISTRATION: Administer ACTIVASE® as soon as possible after the onset

of symptoms.

ACTIVASE® is for intravenous administration only.

The recommended dose is 100 mg administered as 60 mg (34.8 million IU) in the first hour (of which 6 to 10 mg is administered as a bolus over the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 mg (11.6 million IU) over the third hour. For smaller patients (less than 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.8

A DOSE OF 150 MG OF ACTIVASE® SHOULD NOT BE USED BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Although the use of anticoagulants and antiplatelet drugs during and following administration of ACTIVASE® has not been shown to be of unequivocal benefit, heparin has been administered concomitantly for 24 hours or longer in more than 90% of patients. Aspirin and/or dipyridamole have been given either during and/or following heparin treatment.

Reconstitution and Dilution DO NOT USE IF VACUUM IS NOT PRESENT.

ACTIVASE® should be reconstituted by apprincipally adding the appropriate values of the appropriate.

ACTIVASE\* should be reconstituted by asptically adding the appropriate volume of the accompanying Sterile Water for Injection, USP to the vial. It is important that ACTIVASE\* be reconstituted only with Sterile Water for Injection, USP without preservatives. Do not use Bacteriostatic Water for Injection, USP the reconstituted preparation results in a colorless to pale yellow transparent solution containing ACTIVASE\* 10 mg/mL at approximately pH 73. The osmolality of this solution is approximately

215 mOsm/kg.
215 mOsm/kg.
Because ACTIVASE\* contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution may be used for intravenous administration within 8 hours following reconstitution when stored between 2-30°C. Before further dilution or administration, the product should be visually inspected for particulate matter and discoloration prior to administration whenever solution and

container permit.

ACTIVASE\* is stable for up to 8 hours in these solutions at room temperature. Exposure to light has no effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, e.g., Sterile Water for Injection, USP or preservative-containing solutions for further dilution.

No other medication should be added to infusion solutions containing ACTIVASE\*. Any unused interest solutions containing ACTIVASE\*.

infusion solution should be discarded.

HOW SUPPLIED: ACTIVASE® is supplied as a sterile, lyophilized powder in 20 mg and 50 mg vials containing vacuum, each packaged with diluent for reconstitution.

Storage Store lyophilized ACTIVASE® at controlled room temperature not to exceed 30°C (86°F), or under refrigeration (2-8°C/36-46°F). Protect the lyophilized material during extended storage from excessive exposure to light.

Do not use beyond the expiration date stamped on the vial.

ACTIVASE®, Alteplase, recombinant

GENENTECH® INC

460 Point San Bruno Blvd South San Francisco, CA 94080

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#### **Cardiac Transplantation in Patients with Preexisting Neoplastic Diseases**

Brooks S. Edwards, MD, Sharon A. Hunt, MD, Michael B. Fowler, MD, Hannah A. Valantine, MD, Edward B. Stinson, MD, and John S. Schroeder, MD

Cardiac transplantation has traditionally been reserved for individuals with end-stage congestive heart failure (CHF) in whom there is no history of other life-threatening systemic disorders. In most transplant centers, patients with a history of malignancy and severe heart failure have not been considered acceptable candidates for cardiac transplantation. In the last 4 years at Stanford University Medical Center, 8 cardiac transplants have been performed in 7 patients with a history of neoplastic disease. Six of these patients had already received treatment for lymphoproliferative disorders and in 1 case, a patient underwent a transplant after treatment for adenocarcinoma of the colon. Six of the 7 patients were discharged from the hospital and in that group, the 1-year posttransplant survival rate was 71%. This was comparable to an overall 1-year survival rate of 80% for patients undergoing a cardiac transplant at our center during the same period of time. At follow-up averaging over 2 years, there has been 1 case of recurrent neoplasia. One patient with evidence of radiation-induced pulmonary damage died of respiratory failure 2 days after transplantation. One patient required retransplantation because of intractable rejection and subsequently died from infectious complications. Immunosuppressive therapy in these patients has not been associated with an increased risk for neoplastic recurrence or for the development of posttransplant lymphoproliferative disorders. The current study demonstrates that in a carefully selected group, previously treated neoplastic disease should not represent a contraindication to cardiac transplantation.

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or individuals with end-stage congestive heart failure (CHF), cardiac transplantation represents the best therapeutic option for symptomatic improvement and a longer life expectancy.1 However, because of the extreme shortage of donor organs, transplantation can only be applied to a fraction of suitable recipients. To best use this limited resource, recipient selection criteria have traditionally been restrictive.2 CHF may occur in patients who have already received treatment for neoplastic diseases. In these patients, CHF often results from doxorubicin cardiotoxicity or radiation-induced coronary artery disease. Because of the fear that mandatory immunosuppressive therapy might result in recurrence of the neoplasm or a second primary tumor, our group and others 1,2 have previously considered patients with a history of malignancy as high risk and, therefore, unacceptable transplant candidates.

Based on encouraging results in patients who have undergone renal transplantation after diagnosis of a malignancy,3 it was decided at Stanford University in 1985 to proceed with cardiac transplantation in a limited series of patients who have already received treatment for neoplastic diseases and who were considered "cured" of their malignancy. Patients have been selected on an individual basis after careful evaluation of both their cardiovascular status and their risk of recurrent neoplasia. At this time a total of 8 cardiac transplants have been performed in 7 patients. The purpose of this study is to review the clinical results in this group.

The patient characteristics and results are summarized in Table I.

Case 1: A 121/2-year-old boy presented with a 4-year history of progressive CHF. At age 7 the patient was diagnosed as having stage III Burkitt's lymphoma. He received an 18-month course of chemotherapy that included doxorubicin (total dose, 475 mg/m²). Fourteen months after completion of chemotherapy, a radionuclide angiogram showed an ejection fraction of 22%. He had been disease-free from the Burkitt's lymphoma for over 4 years and was considered "cured."

Because of class IV symptoms of CHF on therapy, he underwent cardiac transplantation. During 2 years of follow-up since the transplant, he has suffered only from moderate growth retardation. Immunosuppressive therapy includes cyclosporine, azathioprine and alternateday corticosteroids.

Case 2: An 18-year-old woman was referred for consideration for cardiac transplantation because of a 7year history of progressive symptoms of CHF. At age 9

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**TABLE I** Patient Characteristics and Current Status

Case	Neoplasm	Age at Time of Neoplasm (yrs)	Etiology of CHF	Age at Tx (yrs)	Interval from Neoplasms to Transplant (yrs)	Follow-Up After Tx (yrs)	Tumor Recurrence	Outcome
1 2 3 4 5	Burkitt's Lymphoma Hodgkin's Hodgkin's ALL	7 9 23 17 6	Dox Dox RAD-CAD RAD-CAD Dox	12½ 18 35 37 19	4 7 12 20 4 3 <sup>1</sup> / <sub>4</sub>	2 1½ 4 2¾ 0.5 1½	0 0 0 0 0	Asymptomatic Asymptomatic Asymptomatic Asymptomatic Dead/sepsis Dead/cancer
<ul><li>6</li><li>7</li></ul>	Adenocarcinoma colon Hodgkin's	21	A-CAD RAD-CAD	39	18	0	O recurrence: RAD-C	Dead/RF  AD = radiation-induce

ALL = acute lymphoblastic leukemia; A-CAD = atherosclerotic coronary artery disease; Dox = doxorubicin cardiomyopathy; NR = no recurrence; RAD-CAD = radiation-induced coronary artery disease; RF = respiratory failure; Tx = transplant.

she had stage IV lymphoblastic lymphoma and received a 2-year course of chemotherapy (including a 395 mg/ m2 total dose of doxorubicin) as well as cranial and spinal irradiation (3,000 rads to each field). Because of progressive congestive heart failure despite aggressive medical therapy, she underwent cardiac transplantation. In the 18 months since transplantation, she has had an unremarkable course with no evidence of recurrent neoplastic disease.

Case 3: A 34-year-old woman presented with evidence of myocardial ischemia and severe CHF. Coronary angiography demonstrated diffuse coronary arterial disease consistent with radiation-induced coronary arteriosclerosis. Eleven years earlier at age 23, she had been treated for stage IIB Hodgkin's disease. Treatment consisted of chemotherapy (without doxorubicin) and radiation. One year after completion of therapy, a left lung mass developed. This resolved after it was treated with localized radiation (3,000 rads). She developed progressive intractable symptoms of heart failure and underwent cardiac transplantation at age 35.

The immediate postoperative course was complicated by pulmonary hypertension and right-sided heart failure which were presumably secondary to radiationrelated changes in pulmonary function. The patient was discharged from the hospital on the forty-fourth postoperative day. In follow-up (now 4 years) since cardiac transplantation, she is considered to be in functional class I with no evidence of recurrent neoplastic disease.

Case 4: A 37-year-old man sustained a large anterior myocardial infarction while participating in a rodeo. He rapidly developed cardiogenic shock requiring inotropic support and mechanical ventilation. A coronary arteriogram showed total occlusion of the left main coronary artery. The distal coronary arteries had the appearance of radiation-induced arteriosclerosis. Twenty years before, he had been diagnosed as having stage IIB Hodgkin's disease. He had received radiation therapy to the mediastinum (4,100 rads), axillae (3,945 rads) and supraclavicular fossa (4,103 rads).

This patient underwent cardiac transplantation because of intractable cardiac failure and uncontrollable ventricular arrhythmias. His postoperative course was unremarkable and he was discharged from the hospital on the thirty-first postoperative day. He is currently

asymptomatic 23/4 years after cardiac transplantation with no evidence of recurrent Hodgkin's disease and has returned to the rodeo circuit.

Case 5: A 19-year-old man was referred for transplantation evaluation with a 10-year history of increasing symptoms of CHF. At age 6 he had been diagnosed as having acute lymphoblastic leukemia and was treated with combinations of chemotherapy (including doxorubicin, total dose unknown) and radiation therapy. Between the ages of 6 and 14 he had 4 episodes of bone marrow or testicular recurrence. At the time of transplant evaluation he had been in complete remission for 4 years. Bone marrow examination at that time failed to reveal any evidence of leukemic cells.

At age 19, with symptomatic CHF at rest, he underwent cardiac transplantation. The postoperative period was complicated by recurrent episodes of severe rejection, despite treatment with cyclosporine, azathioprine, oral intravenous corticosteroids and OKT3 monoclonal antibody. Four and one-half months after transplantation because of severe CHF temporary left and right ventricular assist devices were placed and 3 days later, he underwent retransplantation. The postoperative period was complicated by hepatic and renal insufficiency and on the twenty-second postoperative day, he died from aspergillus sepsis. At autopsy, no evidence of malignant disease was found.

Case 6: A 47-year-old man presented with a 9-year history of ischemic heart disease manifest by recurrent infarction, ventricular arrhythmias and CHF. Seven years before, he had undergone coronary artery bypass grafting and 3 years before, the patient underwent a right hemicolectomy for Duke stage C2 adenocarcinoma of the colon. Five of 31 lymph nodes contained a tumor. Treatment included radiation to the pelvis (4,350 rads), abdomen (4,980 rads) and liver bed (2,175 rads).

In addition to routine tests, pretransplant evaluation included abdominal computerized tomography and colonoscopy, both of which failed to demonstrate evidence of neoplastic disease. Three years and 3 months after colonic resection, the patient underwent cardiac transplantation. Postoperative immunosuppression included cyclosporine, azathioprine, prednisone and prophylactic OKT3 monoclonal antibody.

Sixteen months after transplantation and 4¾ years after hemicolectomy, the patient presented with back pain that was found to be due to an epidural mass. Biopsy revealed a tumor consistent with metastatic adenocarcinoma from the colon. The patient subsequently developed spinal cord compression and died of respiratory failure 18 months after transplantation.

Case 7: A 39-year-old man presented to an emergency room with an acute inferior and right ventricular myocardial infarction, completed by shock and hypoxemia. Eighteen years before, he had received radiation to the chest (dose unknown) for stage IIB Hodgkin's disease. An emergency left ventriculogram showed severe inferior dyskinesis. The midportion of a dominant right coronary artery was occluded. Using streptokinase and coronary angioplasty, patency of the right coronary artery was established. However, this was unassociated with hemodynamic improvement. The patient deteriorated and later that day, a cardiac transplant was performed. The patient required inotropic support and afterload reduction to be weaned from the cardiopulmonary bypass; the severe preoperative hypoxia failed to improve. Two days after the transplant, the patient had cardiac arrest and died.

At autopsy, the cardiac allograft was normal. There was gross evidence of acute multifocal pneumonia. Microscopic examination of the lungs showed evidence of prior radiation with apical fibrosis and pleural thickening. The pulmonary vessels displayed myointimal thickening consistent with prior radiation and the airspaces had areas of irregular emphysema with fibrosis. There were extensive alveolar infiltrates composed of neutrophils, macrophages and fibrin. There was no evidence of recurrent Hodgkin's disease.

#### DISCUSSION

This report details the clinical course of 7 patients with a history of neoplastic disease in whom cardiac transplantation has been used to treat end-stage CHF. The 1-year overall survival rate for this select group was 57%. Six of the 7 patients were discharged from the hospital following the transplant, and for this group, the 1-year survival rate was 71%. This compares to the overall 1-year survival rate of 80% for all patients undergoing cardiac transplantation at Stanford during the same period. Among the surviving patients there has been a dramatic improvement in functional status with all patients currently considered to be in New York Heart Association functional class I.

Among the 6 patients discharged from the hospital and treated with long-term immunosuppressive therapy, there was only 1 in whom the neoplasm reoccurred. Although the role of chronic immunosuppression in "permitting" recurrence of disease is difficult to evaluate, it is doubtful that the recurrent colon cancer in this patient was the result of immunosuppressive therapy since adenocarcinoma of the colon is not a malignancy associated with impaired immunosurveillance. There has been no evidence of neoplastic recurrence to date among the patients who underwent transplantation with lymphoproliferative disorders.

The application of cardiac transplantation to these "high-risk" patients has been limited since many transplant centers consider patients with a history of neoplastic diseases unacceptable candidates. In addition to concern that the original malignancy may recur, there has also been concern that the patients may have residual systemic disorders resulting from chemotherapy or radiation and that these factors may adversely affect the patients' prognosis. Indeed, our case 7 illustrates an example in which survival was not limited by neoplastic disease, but by radiation-induced pulmonary parenchymal and vascular disease. The noncardiac systemic effects of chemotherapy and radiation need to be completely evaluated before a transplant.

Recently, Arico,<sup>5</sup> Goenen<sup>6</sup> and their co-workers have reported individual cases of successful cardiac transplantation in patients with doxorubicin cardiomyopathy. At follow-up of 7 and 9 months, both patients continue to do well. Armitage et al<sup>7</sup> have reported preliminary results in a series of 10 patients who have undergone transplantation after documentation of neoplastic diseases. During follow-up, which averages almost 1 year, there has been no evidence for recurrent neoplastic dis-

ease in their group.

As cure rates for hematologic and solid tumors improve and the use of cardiotoxic therapies increase, the occurrence of CHF in cancer patients may represent an increasingly common reason for transplant referral. The concern that these patients may be at increased risk for recurrent or de novo lymphoproliferative disorders does not appear to be supported in the current series. Among the 6 patients discharged from the hospital with an average follow-up period of over 2 years, there have been no cases of posttransplant or recurrent lymphoma. The recurrent colon carcinoma in patient 6 could have been part of the natural history of the patient's disease or could have been due to the institution of systemic immunosuppression. This case illustrates the importance of careful oncologic evaluation of the potential risk of malignant disease recurrence as part of the transplant evaluation process. In retrospect, this patient might be considered a poor choice for transplantation because of the advanced stage of his malignant disease.

This series demonstrates that in carefully selected patients, a history of neoplastic disease need not serve as a contraindication to cardiac transplantation. Risks in these patients include not only recurrent neoplastic disease, but also systemic disorders arising as a result of antineoplastic therapy. To ensure optimal success, these patients require extensive pretransplant evaluation and careful selection. Cardiac transplantation may be well tolerated and provide dramatic improvement in functional status and life expectancy. During acute follow-up, recurrent neoplastic disease after transplantation appears unlikely with careful patient selection. Continued follow-up and increased clinical experience will be required to ensure these encouraging results continue.

**Addendum:** Since submission of the manuscript, 2 additional patients with preexisting neoplasms have undergone cardiac transplantation. One patient, a 14-year-

old boy with a bilateral retinoblastoma and doxorubicin-induced cardiomyopathy, underwent successful cardiac transplantation. The second, a 21-year-old man with a primary undifferentiated mesenchymal tumor of the thorax and combined doxorubicin/radiation-induced cardiotoxicity, underwent cardiac transplantation. In short-term follow-up there has been no recurrence of the primary tumor or de novo occurrence of a secondary neoplasm. Continued long-term follow-up will be required to ensure maintenance of these early favorable results.

Acknowledgment: The authors gratefully acknowledge the invaluable assistance of the transplant coordinators, Patricia Gamberg, RN, and Joan Miller, RN, and the secretarial assistance of Shelly O'Groske.

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# VASOSELECTIVE CAICACHE (nicardipine HCI)

Relaxes the vessels without reducing cardiac output



At therapeutic doses, Cardene relaxes vascular smooth muscle without adversely affecting cardiac contractility\* or AV conduction.

\*C ARDENE does, however, have a negative inotropic effect in some patients with severe left ventricular dysfunction and could, in patients with very impaired function, lead to worsened failure.



decreases NTG consumption.

Efficacy in hypertension<sup>†</sup>

Reduces total peripheral resistance. Longterm efficacy demonstrated in a two-year clinical study.1

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#### **EFFECTS OF VARIOUS CALCIUM ANTAGONISTS**

	CARDENE	Nifedipine	Diltiazem	Verapamil
VASOSELECTIVITY	++++.	+++	+	0
Systemic Vasodilation	++	++	+	+
Vasodilatory Side Effects	++	+++	+	+
Myocardial Depression	0	+	+	+++
Blocks AV Conduction	0	0	+	++
Nonvascular Smooth Muscle Side Effects	0	0	+	+++*
Safe for Concomitant Use W/ß-blockers	+++	11		0
	Systemic Vasodilation Vasodilatory Side Effects  Myocardial Depression  Blocks AV Conduction  Nonvascular Smooth Muscle Side Effects  Safe for Concomitant Use	VASOSELECTIVITY ++++  Systemic Vasodilation ++  Vasodilatory Side Effects ++  Myocardial Depression 0  Blocks AV Conduction 0  Nonvascular Smooth Muscle Side Effects 0  Safe for Concomitant Use	VASOSELECTIVITY  +++  Systemic Vasodilation  ++  Vasodilatory Side Effects  ++  Myocardial Depression  0  +  Blocks AV Conduction  0  Nonvascular Smooth Muscle Side Effects  0  0  Safe for Concomitant Use	VASOSELECTIVITY ++++ +++ +  Systemic Vasodilation ++ ++ ++ +  Vasodilatory Side Effects ++ ++ ++  Myocardial Depression 0 + +  Blocks AV Conduction 0 0 +  Nonvascular Smooth Muscle Side Effects 0 0 0 +  Safe for Concomitant Use

alues are based on a scale from 0 to ++++, where 0= least and ++++= most. \*Particularly, constipation in the elderly

Adapted from Pepine

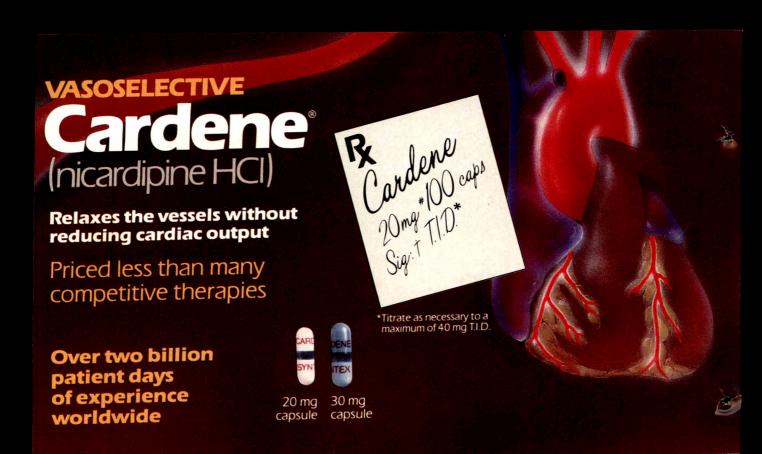
†Due to peak/trough variability with CARDENE, it is consistent with good medical practice to measure blood pressure at trough (8 hours after dosing) and at peak (1–2 hours after dosing). During clinical trials, peak effects of CARDENE were not associated with increased side effects. With CARDENE treatment, blood pressures were significantly reduced throughout the dosing interval compared to placebo.

\*Most common side effects include flushing, headache, dizziness and pedal edema,

Please see brief summary of prescribing information on last page of this advertisement

Inicardipine HCI

Relaxes the vessels without reducing cardiac output



#### **Brief Summary**

#### Cardene® (nicardipine HCI)

For oral use

MECHANISM OF ACTION: CARDENE is a calcium entry blocker which inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle without changing serum calcium concentrations. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. The effects of CARDENE are more selective to vascular smooth muscle than cardiac muscle, in animal models, CARDENE produces relaxation of coronary vascular smooth muscle at drug levels which cause little or no negative inotropic effect.

CONTRAINDICATIONS: Patients with hypersensitivity to the drug. Because part of the effect of CARDENE is secondary to reduced afterload, the drug is also contraindicated in patients with advanced aortic stenosis.

WARNINGS: Increased Angina: About 7% of patients in short term placebo-controlled angina trials have developed increased frequency, duration or severity of angina on starting CARDENE or at the time of dosage increases, compared with 4% of patients on placebo. Comparisons with betablockers also show a greater frequency of increased angina, 4% vs 1%. The mechanism of this effect has not been established. (See ADVERSE REACTIONS.)

established. (See ADVENSE HEACTIONS.)

Use in Patients with Congestive Heart Failure: Although preliminary hemodynamic studies in patients with congestive heart failure have shown that CARDENE reduced afterload without impairing myocardial contractility, it has a negative inotropic effect in vitro and in some patients. Caution should be exercised when using the drug in congestive heart failure patients, particularly in combination with a beta-blocker.

Beta-Blocker Withdrawal: CARDENE is not a beta-blocker and gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal shou be by gradual reduction of the dose of beta-blocker, prefe

ably over 8-10 days.

PRECAUTIONS: General: Blood Pressure:
Careful monitoring of blood pressure during the initial administration and titration of CARDENE is suggested.
CARDENE may occasionally produce symptomatic hypotension. Caution is advised to avoid systemic hypotension when administering the drug to patients who have sustained an acute cerebral infarction or hemorrhage. Because of prominent effects at the time of peak blood levels, initial titration should be performed with measurements of blood

pressure at trough (just before the next dose) and at peak effect (1-2 hours after dosing).

Use in patients with impaired hepatic function: The drug should be used with caution in patients having impaired liver function or reduced hepatic blood flow. Patients with severe liver disease developed elevated blood levels (4-fold increase in AUC) and prolonged halfife (19 hours) of CARDENE.

Use in patients with impaired renal function: Mean plasma concentrations, AUC, and Cmax were approximately 2-fold higher in hypertensive mildly renally impaired patients treated with CARDENE than in healthy controls. Doses in these patients must be adjusted.

Drug Interactions: Cimetidine: Cimetidine increases CARDENE plasma levels. Patients receiving the two drugs concomitantly should be carefully monitored.

Digoxin: Some calcium blockers may increase the concentration of digitalis preparations in the blood. CARDENE usually does not after the plasma levels of digoxin, however, serum digoxin levels should be evaluated after concomitant therapy with CARDENE is initiated.

Maalox: Co-administration of Maalox TC had no effect on CARDENE absorption.

Fentanyl Anesthesia: Severe hypotension has been reported during fentanyl anesthesia with concomitant use of a beta-blocker and a calcium channel blocker. Even though such interactions were not seen during clinical studies with CARDENE, an increased volume of circulating fluids might be required if such an interaction were to occur.

Cyclosporine: Concomitant administration of nicardipine and cyclosporine results in elevated plasma cyclosporine levels. Plasma concentrations of cyclosporine should therefore be closely monitored, and its dosage reduced accordingly, in patients treated with nicardipine.

When therapeutic concentrations of furosemide, propranolol, dipyridamole, warfarin, quinidine, or naproxen were added to human plasma (in vitro), the plasma protein binding of CARDENE was not altered.

Pregnancy: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. CARDENE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is recommended that women who wish to breast-feed should not take this drug.

Pediatric Use: Safety and efficacy in patients under the age of 18 have not been established.

or is nave not been established. **Use in the Elderly:** Pharmacokinetic parameters did not differ between elderly hypertensive patients (≥65 years) and healthy controls after one week of CARDENE 20 mg TID. Plasma CARDENE concentrations in elderly hypertensive patients were similar to plasma concentrations in healthy young adult subjects when CARDENE was adminished.

istered at doses of 10, 20 and 30 mg TID, suggesting that the pharmacokinetics of CARDENE are similar in young and elderly hypertensive patients. No significant differences in responses to CARDENE have been observed in elderly actions and the general adult progulation of noticets when patients and the general adult population of patients who participated in clinical studies.

participated in clinical studies.

ADVERSE REACTIONS: In short-term (up to three months) studies 1,910 patients received CARDENE alone or in combination with other drugs. In these studies, adverse events were generally not serious but occasionally required dosage adjustment. Peak responses were not observed to be associated with adverse effects during clinical trials, but physicians should be aware that adverse effects associated with decreases in blood pressure (tachycardia. hypotension. with decreases in blood pressure (tachycardia, hypotension, etc.) could occur around the time of the peak effect.

etc.) could occur around the time of the peak effect.

Angina: The most common adverse events include pedal edema and dizziness in about 7% of patients; headache, asthenia, flushing and increased angina in about 6%; palpitations in about 3%; and nausea and dyspepsia in about 2%. Adverse events occurring in about 1% of patients include dry mouth, somnolence, rash, tachycardia, myalgia, other edema and paresthesia. Sustained tachycardia, syncope, constipation, dyspnea, abnormal ECG, malaise, nervousness and tremor occurred in less than 1% of patients. In addition, adverse events were observed which are not

ness and tremor occurred in less than 1% or patients. In addition, adverse events were observed which are not readily distinguishable from the natural history of the atherosclerotic vascular disease in these patients. Adverse events in this category each occurred in < 0.4% of patients receiving CARDENE and included myocardial infarction, atrial fibrillation, exertional hypotension, pericarditis, heart block, cerebral ischemia and ventricular tachycardia. It is possible that some of these events were drug-related.

possible that some of these events were drug-related.

Hypertension: The most common adverse events include flushing in about 10% of patients; headache and pedal edema in about 8%; asthenia, palpitations and dizziness in about 4%; tachycardia in about 3%; nausea in about 2%; and somnolence in 1%. Dyspepsia, insomnia, malaise, other edema, abnormal dreams, dry mouth, nocturia, rash and vomiting occurred in less than 1% of patients.

Additionally the following rare events have been reported:

vomiting occurred in less than 1% of patients. Additionally, the following rare events have been reported: infection, allergic reaction, hypotension, postural hypotension, atypical chest pain, peripheral vascular disorder, ventricular extrasystoles, ventricular tachycardia, sore throat, abnormal liver chemistries, arthralgia, hot flashes, vertigo, hyperkinesia, impotence, depression, confusion, anxiety, rhinitis, sinusitis, tinnitus, abnormal vision, blurred vision, increased urinary frequency. increased urinary frequency.

More detailed professional information available on request.

U.S. Patent No. 3,985,758

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## Normal Values for Noninvasive Estimation of Left Ventricular Contractile State and Afterload in Children

Rodney C.G. Franklin, MRCP, Richard K.H. Wyse, PhD, Thomas P. Graham, MD, Vanda M. Gooch, BSc, and John E. Deanfield, MRCP

The outcome and suitability for therapeutic interventions in children with congenital heart disease depend frequently on left ventricular function. Congenital heart disease is characterized by changes in loading conditions, making it difficult to assess ventricular contractility using conventional load-dependent indexes. Two-dimensional and M-mode echocardiography and arterial blood pressure were used to study left ventricular morphometrics and contractility in 44 normal children, aged 2 to 12 years. Left ventricular end-systolic and end-diastolic length, diameter, wall thickness, volume and mass all showed linear increases with body surface area (p <0.001 in all). Shortening and ejection fractions, velocity of circumferential fiber shortening, morphometric ratios and endocardial meridional and circumferential stress (mean 46 and 115 g/cm², respectively) all remained constant. A load-independent measure of the normal resting left ventricular contractile state was determined by relating the rate-corrected velocity of circumferential fiber shortening to end-systolic endocardial meridional and circumferential stress; there was an inverse linear correlation (r = -0.641 and -0.557 respectively, p <0.001). These data provide a quantitative basis for assessment of myocardial hypertrophy, afterload and contractile state in childhood.

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eft ventricular function frequently influences the choice and timing of cardiac surgery, as well as long-term survival, in children with congenital heart disease. 1,2 Abnormalities of ventricular shape, hypertrophy and loading conditions exist and may be altered by medical and surgical interventions. Thus, the commonly used load-dependent indexes of systolic function, such as ejection fraction, may be difficult to interpret. Colan et al<sup>3</sup> have described a sensitive echocardiographic measure of left ventricular contractility, which is relatively independent of loading. Studies of the estimation of afterload (end-systolic stress) and contractile state, however, have either involved few subjects or have not been targeted at the age range over which definitive surgery is usually undertaken.3-7 Our purpose was to determine normal pediatric values for left ventricular morphometrics, end-systolic stress and contractility over this age range for comparison with children who have established or suspected heart disease.

#### **METHODS**

**Patients:** We studied 44 normal prepubertal children (22 boys, 22 girls) with no symptoms or signs of cardiovascular disease (including normal blood pressure), and 2-dimensional echocardiograms. They were 2 to 12.7 years old (median age 6.8 for boys and 6.5 for girls).

Echocardiography: An Advanced Technology Laboratory Mark 600 ultrasound system with 3.5- or 5.0-MHz transducers was used to study subjects in a supine or a slight left lateral decubitus position. Left ventricular length (apex to midpoint of mitral valve anulus) at end-diastole (onset of QRS) and end-systole (first highfrequency component of second heart sound) was measured from an apical 4-chamber view with the transducer angulated to minimize foreshortening. Hard copies of M-mode recordings were made of the left ventricular anterior-posterior diameter (at the tips of the mitral valve leaflets), with simultaneous phonocardiograms and carotid pulse tracings. Left ventricular internal dimension, length and posterior wall thickness were then measured at end-diastole and end-systole for 5 beats and mean values computed (Figure 1). Left ventricular ejection time was calculated from the carotid pulse tracing and rate corrected to a heart rate of 60 beats/min by dividing by |RR interval (Figure 1). Endsystolic pressure was estimated by assigning the noninvasively obtained peak systolic blood pressure to the peak and diastolic pressure to the nadir of the carotid pulse, with subsequent linear interpolation to the level of the incisura.8

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TABLE I Anthropomorphic Data and Pressures in 44 **Patients** 

Patients		
	Mean ± SD	Range
Age (yrs) Weight (kg) Body surface area (m²) Systolic BP (mm Hg) Diastolic BP (mm Hg) Pes (mm Hg) Heart rate (beats/min)	$6.7 \pm 3.2$ $22.1 \pm 7.4$ $0.83 \pm 0.21$ $104 \pm 9.0$ $61 \pm 8.5$ $82 \pm 8.4$ $93 \pm 13$	2.0 to 12.7 11.3 to 39.3 0.5 to 1.29 80 to 126 44 to 80 59 to 100 67 to 127
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BP = blood pressure; Pes = estimated end-systolic pressure; SD = standard

Dimensional and velocity data: Shortening fraction and the rate-corrected velocity of circumferential fiber shortening at the endocardium and mid-wall were determined, as we have previously described.9

Ratios of wall thickness and length to minor axis diameter at end-systole and end-diastole were evaluated to assess any change in chamber size and shape with growth.

Volume and mass data: Left ventricular end-diastolic and end-systolic volumes were calculated using a modification of the ellipsoid biplane method, 10 regarding the left ventricular minor axis as circular and assuming a prolate ellipsoid left ventricular topology. Stroke volume, ejection fraction and cardiac index were determined. Left ventricular wall mass was calculated by a modification of the cube method, with measurement rather than assumption of ventricular length.9

Wall stress: Endocardial and mid-wall end-systolic wall stresses in the meridional and circumferential directions were calculated, using formulas that we have previously detailed.9 Mid-wall circumferential stress was calculated by the formula described by Mirsky.11

Statistical analysis: Data were stored in a SIR (version 2) database on an Amdahl mainframe computer and analyzed with SAS and SPSS (version 10) statistical packages. Inter- and intraobserver variability were assessed for all variables for 5 cardiac cycles in each of 6 subjects. The coefficients of variation for interobserver variability were 0.2 to 4.7% and 0.5 to 3.2% for intraobserver variability for each of the measured variables. All data were expressed as mean ± standard deviation. Shortening fraction, ejection fraction and rate-corrected velocity of circumferential fiber shortening were related to indexes of wall stress using linear regression analysis.

#### RESULTS

None of the variables or derived indexes (Tables I, II and III) showed any significant sex differences.

Left ventricular dimensions, shape and mass: The relation between left ventricular end-systolic and enddiastolic diameters, volumes (Figure 2) and wall thickness with body surface area were best described as a positive linear function (best fit), reflecting growth (Table II). The correlations with body surface area were stronger than with age, weight or height. They were not improved as a log, square root or cube root function of body surface area, reflecting the fact that the age range studied did not include the rapid growing periods of infancy or puberty. Left ventricular mass also increased linearly with body surface area (r = 0.864, p < 0.001). During a period of cardiac growth, in which left ventricular mass increased by 350%, there was no change in left ventricular topology. The ratios of length to diameter, wall thickness to diameter and volume to mass all remained constant (Table III).

Load-dependent indexes: Shortening fraction, ejection fraction, cardiac index and all calculations of velocity of circumferential fiber shortening (rate and nonrate

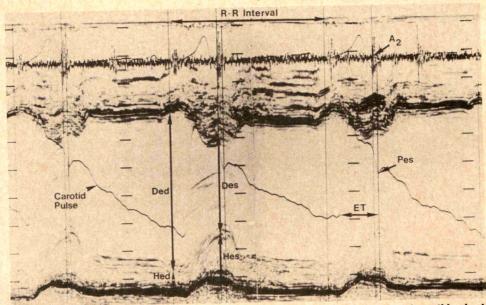


FIGURE 1. Detail of M-mode tracing with simultaneous electrocardiograph, phonocardiograph and carotid pulse tracing showing the indexes measured. The vertical lines were drawn in to identify end-diastole (onset of QRS), end-systole (phonocardiographic A<sub>2</sub>) and end-systolic pressure (Pes, dicrotic notch of carotid pulse tracing). The bottom horizontal line indicates the incisura used for deriving Pes (see text). Ded = end-diastolic diameter; Des = end-systolic diameter; ET = ejection time; Hed = end-diastolic posterior wall thickness; Hes = end-systolic posterior wall thickness.

**TABLE II** Means ± Standard Deviations and Ranges of Measured and Calculated Morphometric Variables with Linear Regression Equations and Correlations Against Body Surface Area in 44 Patients

	Mean ± SD	Range	Linear Regression Equation	r vs BSA
Ded (cm) Des (cm) Hed (cm) Hes (cm) Led (cm) Les (cm) ETc (ms) EDV (cm)	$3.68 \pm 0.48$ $2.38 \pm 0.35$ $0.56 \pm 0.09$ $1.04 \pm 0.12$ $6.46 \pm 0.99$ $5.26 \pm 0.94$ $0.35 \pm 0.02$	2.95 to 4.83 1.74 to 3.40 0.43 to 0.78 0.67 to 1.49 4.76 to 9.19 3.56 to 7.93 0.30 to 0.40	y = 1.86 (BSA) + 2.14 y = 1.22 (BSA) + 1.37 y = 0.29 (BSA) + 0.32 y = 0.58 (BSA) + 0.54 y = 3.73 (BSA) + 3.01 y = 3.40 (BSA) + 2.15 y = -0.50 (BSA) + 0.39	0.823* 0.738* 0.673* 0.633* 0.675* 0.647*
EDV (ml) ESV (ml) SV (ml) LV mass (g)	$47.5 \pm 17.7$ $16.3 \pm 6.8$ $31.2 \pm 11.3$ $49.6 \pm 18.7$	22.44 to 107.30 6.69 to 38.94 15.75 to 68.35 22.51 to 95.62	y = 71.5 (BSA) - 12.0 y = 26.0 (BSA) - 5.3 y = 47.7 (BSA) - 10.1 y = 75.7 (BSA) - 13.3	0.863* 0.821* 0.842* 0.864*

Significance of linear correlation: \*p <0.001; †p <0.01. BSA = body surface area; Ded = end-diastolic diameter; Des = end-systolic diameter; EDV = end-diastolic volume; ESV = end-systolic volume; ETc = rate-corrected ejection time; efficient; SV = stroke volume.

corrected, endocardial and mid-wall) were independent of age and body surface area (Table III). Inverse linear (best fit) correlations were found between end-systolic endocardial stress in circumferential and meridional directions and both shortening fraction (r = -0.576, y = -0.0009x + 0.458 and r = -0.618, y = -0.0018x + 0.433, respectively, p <0.001) and ejection fraction (r = -0.588, y = -0.0007x + 0.736 and r = -0.632, y = -0.0011x + 0.709, respectively, p <0.001).

Afterload assessment: Afterload, as estimated by both meridional and circumferential end-systolic wall stress, did not change with age or body surface area over the age range studied. Endocardial circumferential stress was 2.5 times endocardial meridional stress, whereas mid-wall circumferential stress was 1.5 times mid-wall meridional stress.

Load-independent assessment of contractility: The range of the normal left ventricular resting contractile state was determined by relating the rate-corrected velocity of circumferential fiber shortening to end-systolic stress. There were inverse correlations with both circumferential and meridional endocardial end-systolic stress (Figures 3 and 4) but no significant correlations were found between these indexes when all were calculated from mid-wall values.

#### DISCUSSION

The normal data in this study provide a framework for assessing ventricular function in children with acquired or congenital heart disease over the age range at which definitive surgery is usually performed. The value of such data has been demonstrated previously, using smaller aged-matched normal control groups, compared to patients with transposition of the great arteries, 4,7,12 aortic stenosis and coarctation, 5 renal disease 6 and tricuspid atresia. 9

**Limitations:** The limitations of echocardiography when measuring left ventricular dimensions have been reviewed extensively. <sup>13,14</sup> We measured ventricular length, as it is not appropriate to assume that it is twice the cross-sectional diameter, <sup>15</sup> particularly in diseases with a dilated ventricle. However, when calculating left

**TABLE III** Means ± Standard Deviations of Calculated Ratios, Indexes of Systolic Function and Wall Stress with Correlations Against Body Surface Area in 44 Patients

	Mean ± SD	r vs BSA
Led/Ded	1.77 ± 0.25	NS
Les/Des	$2.24 \pm 0.42$	NS
Hed/Ded	$0.15 \pm 0.02$	NS
Hes/Des	$0.45 \pm 0.08$	NS
SV/BSA (ml/m²)	$37.1 \pm 7.4$	NS
CI (liters/min/m²)	$3.4 \pm 0.8$	NS
EDV/mass (ml/g)	$0.97 \pm 0.16$	NS
EF (%)	66 ± 4	NS
SF (%)	35 ± 3	NS
VCF (circ/s)	$1.25 \pm 0.15$	NS
VCFmw (circ/s)	$0.68 \pm 0.11$	NS
VCFc (circ/s)	$1.01 \pm 0.11$	NS
VCFmwc (circ/s)	$0.55 \pm 0.09$	NS
ESSm (g/cm <sup>2</sup> )	45.5 ± 12.4	NS
ESSc (g/cm <sup>2</sup> )	$114.5 \pm 22.2$	NS
ESSmmw (g/cm <sup>2</sup> )	$71.3 \pm 14.1$	NS
ESScmw (g/cm <sup>2</sup> )	$110.3 \pm 17.7$	NS

CI = cardiac index; EF = ejection fraction; ESSc = endocardial end-systolic circumferential wall stress; ESScmw = mid-wall end-systolic circumferential wall stress; ESSm = endocardial end-systolic meridional wall stress; ESSmmw = mid-wall end-systolic meridional wall stress; ESSmmw = mid-wall end-systolic meridional wall stress; NS = difference not significant; SF = shortening fraction; VCF = velocity of circumferential fiber shortening; VCFc = rate-corrected velocity of circumferential vCFmwc = rate-corrected midwall velocity of circumferential fiber shortening; vCFmwc = rate-corrected midwall velocity of circumferential fiber shortening; other abbreviations as in Table II.

ventricular volumes, we assumed that the minor axis cross-section was circular. This is not appropriate in patients with significant right ventricular hypertrophy, which distorts left ventricular geometry. In these patients both the anterior-posterior minor axis diameter and its perpendicular (left to right) axis should be measured (unmodified ellipsoid biplanar method<sup>10</sup>). Although more accurate mass and volume estimations can be provided using Simpson's rule or planimetry, <sup>10,14</sup> this requires multiple cross-sectional images and excellent resolution of the entire left ventricular myocardium. This was not possible in many of our normal subjects and is also the case for many patients. Regional wall motion abnormalities are also a potential source of error. <sup>14</sup> Although less common in children with congeni-

tal heart disease than adults with ischemic heart disease, they must be excluded by 2-dimensional echocar-diography before quantifying left ventricular function with these methods.

Morphometrics: Our measurements of left ventricular growth are in close agreement with published reports. 16-18 There was a small, but significant, increase in end-systolic and end-diastolic ventricular volumes when indexed to body surface area, as we reported in a smaller patient group. 15 The values for older children were similar to those in adults 19: the lower relative ventricular volumes reported in children younger than 2 years using angiographic data 20 are at least partly due to the higher heart rates, which then decrease with age. 21

Similar results, reflecting growth, have been reported for left ventricular mass<sup>16,20</sup> and mass index<sup>22</sup> in children. Adult values, when corrected for body surface

area, have been shown to be higher, <sup>19,23</sup> due to the proportionately greater growth of the heart compared to body surface area when all ages are considered. A contributing factor could be the relative amount of lean body mass. This changes with age. In adult studies, the differences between men and women were no longer significant when using lean body mass rather than body surface area for indexing. <sup>23</sup>

Throughout the age range studied the prolate, truncated ellipsoid shape of the left ventricle, as assessed by length and wall thickness to diameter ratios, remained unchanged. Volume to mass ratios were also constant with results within the normal ranges of published pediatric<sup>22</sup> and adult<sup>19</sup> data. Thus left ventricular mass and volume increase in proportion to each other. This may not be the case in children with congenital heart disease, who may not be able to maintain an appropriate bal-

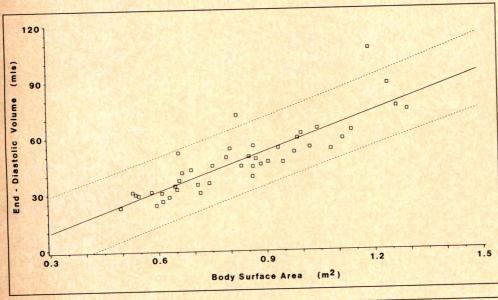


FIGURE 2. Positive linear relation of end-diastolic volume to increasing body surface area: r = 0.863, p <0.001; slope y = 71.5x - 12.0.

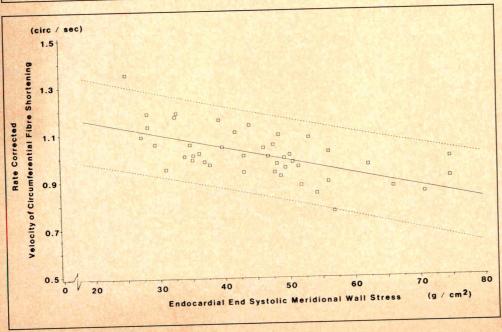


FIGURE 3. Relation of endocardial end-systolic meridional stress to rate-corrected velocity of circumferential fiber shortening, showing an inverse linear correlation: r = -0.641, p < 0.001; slope y = -0.005x + 1.22.

ance between these indexes during cardiac growth, either as part of the natural history of their lesion or because of therapeutic interventions.

Systolic function and contractility: Shortening fraction, ejection fraction and cardiac index all remained unchanged over a wide range of age and heart rates, as previously reported.<sup>17,24</sup> Similarly, all estimates of endsystolic stress (circumferential and meridional, endocardial and mid-wall) were independent of age and body surface area, despite increasing blood pressure. Our results for meridional stress were in close agreement with reports from Colan,25 Borow5 and their co-workers for older patients but are 24% higher than infant values also reported by Colan et al7 (Table IV). Thus an agerelated increase in end-systolic stress is apparent during the first few years of life. Values for circumferential stress were similar to those reported in adults26 and were consistently 1.5 to 2.5 times higher than meridional stress, consistent with left ventricular topology.

Ideally, contractility should be expressed in a way that is independent of preload and afterload. This is best achieved by examining the interactions of indexes of left ventricular function at end-systole.27 The inverse correlations between ejection fraction26 and shortening fraction<sup>3,28</sup> with end-systolic stress are preload dependent.<sup>3</sup> However, by relating stress to the rate-corrected velocity of circumferential fiber shortening, Colan et al3 produced an index that is less dependent on preload and incorporates afterload, heart rate and dimension. It can thus differentiate between changes due to altered loading conditions and those due to a primary myocardial problem, and is applicable to a wide range of conditions and ages. Our results extend the age range reported by Colan et al.3 The similar inverse relation with circumferential wall stress during childhood has not been published previously. Although this may be a more appropriate index to use (as velocity of circumferential fiber

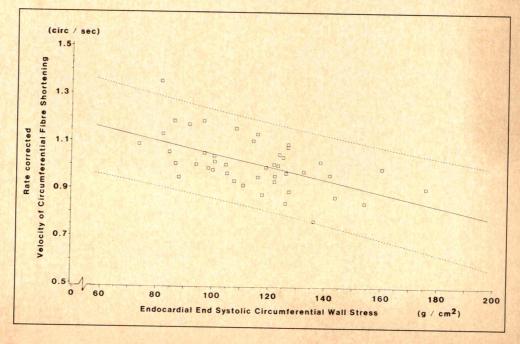
TABLE IV Normal Meridional End-Systolic Stress Values End-Systolic Age Group Pts Stress (yrs) (n) (gm/cm<sup>2</sup>) Reference  $0.09 \pm 0.03$  $38 \pm 6$ Colan et al7  $1.4 \pm 1.1$  $36 \pm 9$ Colan et al7  $6.7 \pm 3.2$ 44  $46 \pm 12$ Present study (2.0 to 12.7)  $16 \pm 10$ 22  $46 \pm 7$ Borow et al5 (6 to 40)  $22 \pm 6$ 33  $52 \pm 10$ Colan et al<sup>37</sup> \* 68 subjects total.

shortening also examines changes in a circumferential direction), the length data required are less easily obtained

Normal mid-wall measurements and resulting indexes of left ventricular function have not previously been reported for children. Such mid-wall data are theoretically more useful for assessing patients with left ventricular hypertrophy,<sup>29</sup> but we found the normal range was narrow, with no high or low values. In addition, we did not find an inverse correlation with mid-wall velocity of circumferential fiber shortening.

While the relation of end-systolic stress to the rate-corrected velocity of circumferential fiber shortening represents the best load-independent index of left ventricular contractility, the measurement of end-systolic stress is time consuming and therefore difficult in routine clinical practice. The rate-corrected velocity of circumferential fiber shortening can be estimated rapidly using a Doppler-derived ejection time. Our normal values  $(1.01 \pm 0.22 \text{ circumference/s}, \text{ mean } \pm 2 \text{ standard deviations})$  can provide a quick estimate of abnormality. From Figure 3, it is clear that values >1.00 circumference/s do not require an estimate of end-systolic stress. Such patients would nearly always have a normal con-

FIGURE 4. Relation of endocardial end-systolic circumferential stress to rate-corrected velocity of circumferential fiber shortening, showing an inverse linear correlation: r = -0.557, p <0.001; slope y = -0.002x + 1.26.



tractile state. End-systolic meridional stress values of approximately 15 gm/cm<sup>2</sup> would be required for such a value to be low. Patients with values <1.00 circumference/s should have end-systolic stress measured for an accurate assessment of contractility.

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#### **HEXABRIX®**

ach milliliter of HEXABRIX contains 393 mg of ioxaglate neglumine, 196 mg of ioxaglate sodium and 0.10 mg edetate alcium disodium as a stabilizer. The solution contains 3.48 mg (0.15 mEq) sodium in each milliliter and provides 32% (320 mg/mL) organically bound iodine.

#### CONTRAINDICATIONS

CONTRAINDICATIONS

HEXABRIX is contraindicated for use in myelography. Refer to 
PRECAUTIONS concerning hypersensitivity. Hysterosalpingography should not be performed during the menstrual 
perdod; in pregnant patients, in patients with known infection 
in any portion of the genital tract, or in patients in whom 
cervical conization or curetage has been performed within 
30 days. Arthorography should not be performed if infection is present in or near the joint.

#### WARNINGS

lonic iodinated contrast media inhibit blood coagulation, in witro, more than nonionic contrast media. Nonetheless, it is prudent to avoid prolonged contact of blood with syringes con taking indig. contrast media.

witro, more than nonlonic contrast media. Nonetheiess, it is prudent to avoid prolonged contact of blood with syringes containing lonic contrast media.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonlonic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state, and concomitant medications may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended including close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinized saline solutions and minimizing the length of the procedure. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of in witro clotting.

As with any contrast medium, serious neurologic sequelae, including permanent paralysis, can occur following cerebral arteriography, selective spinal arteriography and arteriography divessels supplying the spinal gord. The impection of a contrast medium should never be made following the administration of vasopressors, since they strongly portatiate neurologic effects.

In adients with subarachnoid hemorrhage, a rare associa-

logic effects.

In patients with subarachnoid hemorrhage, a rare association between contrast administration and clinical deterioration, including convulsions and death, has been reported. Therefore, administration of intravascular iodinated contrast media in these patients should be undertaken with caution. A definite risk exists in the use of intravascular contrast agents in patients who are known to have multiple myeloma. In such instances anuria has developed, resulting in progressive uremia, renal failure and eventually death. Although neither the contrast agent nor delydration has separately proved to be the such instances anuria has developed, resulting in progressive uremia, renal failure and eventually death. Although neither the cause of anuria in myeloma, it has been speculated that the cause of anuria in myeloma, it has been speculated that the combination of both may be a causative factor. The risk in myelomatous patients is not a contraindication to the procedure; however, partial delydration in the preparation of these patients for the examination is not recommended since this may predispose to precipitation of myeloma protein in the renal tubules. No form of therapy, including dialysis, has been successful in reversing the effect. Myeloma, which occurs most commonly in persons over 40, should be considered before instituting intravascular administration of outsidered before instituting intravascular administration of suspected to have pheochromocytoma should be performed with extreme caution. It, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The blood pressure should be assessed throughout the procedure, and measures for trainent of a hypertensive crisis should be available.

Since intravascular administration of contrast media may promote sickling in individuals who are homozygous for sickle cell disease, fluid restriction is not advised.

In patients with advanced renal disease, iodinated contrast media should be used with caution and only when the need for the examination dictates. Since excretion of the medium may

In patients with advanced renal disease, iconitate united media should be used with caution and only when the need for the examination dictates, since excretion of the medium may be impaired. Patients with combined renal and hepatic disease, those with severe hypertension or congestive heart failure and recent renal transplant recipients present an

additional risk.

Renal failure has been reported in patients with liver
dysfunction who were given an oral cholecystographic agent
followed by an intravascular iodinated radiopaque agent and
also in patients with occult renal disease, notably diabetics and
hypertensives. In these classes of patients there should be no fluid restriction and every attempt made to maintain norm dration prior to contrast medium injection, since dehydra-n is the single most important factor influencing further

renal impairment.
Caution should be exercised in performing contrast medium studies in patients with endotoxemia and/or those with elevated body temperatures.

Reports of thyroid storm occurring following the intravascular use of iodinated radiopaque agents in patients with hyperthyroidism or with an autonomously functioning thyroid nodule, suggest that this additional risk be evaluated before use of this drug, lodine-containing contrast agents may after the results of thyroid function tests which depend on iodine estimation, e.g., PBI, and may also affect results of radioactive iodine uptake studies. Such tests, if indicated, should be performed prior to the administration of this preparation.

#### **PRECAUTIONS**

PRECAUTIONS

Diagnostic procedures which involve the use of iodinated intravascular contrast agents should be carried out under the direction of personnel skilled and experienced in the particular procedure to be performed. All procedures utilizing contrast media carry a definite risk of producing adverse reactions. While most reactions are minor, life-threatening and fatal reactions may occur without warning, and this risk must be weighed against the benefit of the procedure. A fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating adverse reactions of all types should always be available. If a serious reaction should occur, immediately discontinue administration. Since severe delayed reactions have been known to occur, emergency facilities and competent personnel should be available for at least 30 to 60 minutes after administration. (See ADVERSE REACTIONS.)

Preparatory dehydration is dangerous and may contribute to acute renal failure in infants, young children, the elderlipatients with pre-existing renal insufficiency, patients with untiliple myeloma, patients with advanced vascular disease and diabetic patients.

Acute renal failure has been reported in diabetic patients with diabetic nephropathy and in susceptible non-diabetic patients (often elderly with pre-existing renal disease) following the administration of iodinated contrast agents. Therefore, careful consideration of the potential risks should be given before performing this radiographic procedure in these patients. Severe reactions to contrast media often resemble allergic responses. This has promitted the use of several provocative

fore performing this radiographic procedure in these patients. Severe reactions to contrast media often resemble allergic responses. This has prompted the use of several provocative pretesting methods none of which can be relied on to predict severe reactions. No conclusive relationship between severe reactions and antigen-antibody reactions or other manifestations of allergy has been established. The possibility of an idiosyncratic reaction in patients who have previously received a contrast medium without ill effect should always be considered. Prior to the injection of any contrast medium, the patient should be questioned to obtain a medical history with emphasis on allergy and hypersensitivity. A positive history of bronchilad asthma or allergy (including food), a family history of largery, or a previous reaction or hypersensitivity to a contrast agent may imply a greater than usual risk. Such a history may be more accurate than pre-testing in predicting the potential for reaction, although not necessarily the severity or type of reaction in the individual case. A positive history of this type does not arbitrarily contraindicate the use of a contrast agent when a diagnostic procedure is thought essential, but does call for caution. (See ADVERSE REACTIONS.)

Prophylactic therapy including corticosteroids and anti-histamines should be considered for patients who present with a strong allergic history, a previous reaction to a contrast redum, or a positive pre-test since in these patients the incidence of reaction is two to three times that of the general population. Adequate doses of corticosteroids should be started early enough prior to contrast medium injection to be effective and should continue for injection and

dence of reaction is two to times that of the general population. Adequate doses of corticosteroids should be started early enough prior to contrast medium injection to be effective and should continue through the time of injection and for 24 hours after injection. Antihistamines should be administered within 30 minutes of the contrast medium injection. Recent reports indicate that such pre-treatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity. A separate syringe should be used for these injections.

General anesthesia may be indicated in the performance of some procedures in selected patients; however, a higher incidence of adverse reactions has been reported in these patients, and may be attributable to the inability of the patient to identify untoward symptoms or to the hypotensive effect of anesthesia which can prolong the circulation time and increase the duration of contact of the contrast agent.

Angiography should be avoided whenever possible in patients with homocystinuria because of the risk of inducing thrombosis and embolism.

PRECAUTIONS FOR

#### PRECAUTIONS FOR SPECIFIC PROCEDURES

SPECIFIC PROCEDURES
Pediatric Angiocardiography: It is advisable to monitor for ECG and vital signs changes throughout the procedure.
When large individual doses are administered, sufficient time should be allowed for any observed changes to return to or near baseline prior to making the next injection.
Caution should be used when making right heart niections in patients with pulmonary hypertension or incipient heart failure, since this may lead to increased right side pressures with subsequent bradycardia and systemic hypotension. Patients with pulmonary disease present additional risks.
Caution is advised in cynontic infants since apnea, bradycardia, other arrhythmias and a tendency to acidosis are more likely to occur.
Since infants are more likely to respond with convulsions than are adults, the amount of total dosage is of particular importance. Repeated injections are hazardous in infants weighing less than 7 kg, particularly when these infants have pre-existing compromised right heart function or obliterated pulmonary vascular beds.

Selective Coronary Arteriography with ne withhout left.

weighing less than 7 kg, particularly when these infants have pre-existing compromised right heart function or obliterated pulmonary vascular beds. 
Selective Coronary Arteriography with or without left ventriculography. During the administration of large doses of HEXABRIX, continuous monitoring of vital signs is desirable. Caution is advised in the administration of large volumes to patients with incipient heart failure because of the possibility of aggravating the pre-existing condition. Hypotension should be corrected promptly since it may result in serious arrhythmias. Special care regarding dosage should be observed in patients with right ventricular failure, pulmonary hypertension, or stenotic pulmonary vascular beds because of themodynamic changes which may occur after injection into the right heart outflow tract.

Peripheral Arteriography: Moderate decreases in blood pressure occur frequently with intra-arterial (brachial) injections. This change is sually transient and requires no treatment, however, the blood pressure should be monitored for approximately ten minutes following injection.

Extreme caution during injection of the contrast agent is necessary to avoid extravasation and fluoroscopy is recommended. This is especially important in patients with severe arterial disease.

Cerebral Anniography: Cerebral angiography should be

severe arterial disease. Cerebral Angiography: Cerebral angiography should be performed with special caution in patients with advanced arteriosclerosis, severe hypertension, cardiac decompen-sation, senilty, recent cerebral thrombosis or embolism, and

migraine.

Intra-Arterial Digital Subtraction Angiography: The risks associated with IA-DSA are those usually attendant with catheter procedures. Following the procedure, gentle pressure hemostasis is required, followed by observation and immobilization of the limb for several hours to prevent ge from the site of arterial puncture

Patient motion, including respiration and swallowing, can result in misregistration leading to image degradation and

result in misregistration leading to image degradation and non-diagnostic studies. Intravenous Digital Subtraction Angiography: The risks associated with IV-DSA include those usually attendant with catheter procedures and include intramural injections, vessel dissection and tissue extravasation. The potential risk is re-duced when small test injections of contrast medium are made under fluoroscopic observation to insure that the catheter tip is properly positioned and, in the case of peripheral placement, that the vein is of adequate size. Patient motion including respiration and swallowing, can

nat use vent is or acquare size.
Patient motion, including respiration and swallowing, can result in misregistration leading to image degradation and non-diagnostic studies.

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non-diagnostic studies. Peripheral Venography: Special care is required when venography is performed in patients with suspected thrombosis, phlebitis, severe ischemic disease, local infection or a totally obstructed venous system. Extreme caution during injection of contrast media is necessary to avoid extravasation and fluoroscopy is recommended. This is especially important in patients with severe arterial or venous disease.

Excretory Urography: Infants and small children should not have any fluid restrictions prior to excretory urography. (See WARNING and PRECAUTIONS concerning preparatory dehydration.)

Contrast Enhancement in Body Computed Tomography:
Patient cooperation is essential since patient motion, including respiration, can markedly affect image quality. The use of an intravascular contrast medium can obscure tumors in patients undergoing CT evaluation of the liver, resulting in a false negative diagnosis. Dynamic CT scanning is the procedure of choice for malignant tumor enhancement.

Arthorgarby: Strict asspite technique is required to prevent the introduction of infection. Fluoroscopic control should be used to insure proper introduction of the needle into the synovial space and prevent extracapsular injection. Aspiration of excessive synovial fluid will reduce the pain on injection and prevent the dilution of the contrast agent. It is important that undue pressure not be exterted during the injection. Hysterosalpingography: Caution should be exercised in patients suspected of having cervical or tubal carcinoma to avoid possible syread of the lesion by the procedure. Delayed onset of pain and fever (1-2 days) may be indicative of pelvic infection.

Carcinogenesis. Mutagenesis, Impairment of Fertility: No

ewic infection.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No ong-term animal studies have been performed to evaluate arcinogenic potential. However, animal studies suggest that his drug is not mutagenic and does not affect fertility in males

or ternales. Prepanary Category B: Reproduction studies have been performed in rats and rabbits at doses up to two times the maximum adult human dose and have revealed no evidence of impaired ferbility or harm to the fetus due to HEXABRIX. There are, however, no adequate and well controlled studies in pregnant women: Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Nursing Mothers: loxaglate salts are excreted unchanged in human milk. Because of the potential for adverse effects in current indicats, bottle teedings should be substituted for

nursing infants, bottle feedings should be substituted for breast feedings for 24 hours following the administration of

this drug. Pediatric Use: Safety and effectiveness in children has been established in pediatric angiocardiography and intravenous excretory urography. Data have not been submitted to sup-port the safety and effectiveness of HEXABRIX in any other intention of the safety and effectiveness of HEXABRIX in any other

utions for specific procedures receive comment

#### ADVERSE REACTIONS

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and diosyncratic reactions. Chemotoxic reactions and diosyncratic reactions. Chemotoxic reactions result from the physiochemical properties of the contrast media, the dose and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels pertused by the contrast medium are included in this category. Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the dose injected, the speed of injection, the mode of injection and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

mandatory.

NOTE: Not all of the following adverse reactions have been reported with HEXABRIX. Because HEXABRIX is an iodinated intravascular contrast agent, all of the side effects and toxicity associated with agents of this class are theoretically possible, and this should be borne in mind when HEXABRIX is

administered. Szever, life-threatening anaphylactoid reactions, mostly of cardiovascular origin, have occurred following the administration of HEXABRIX as well as other iodine-containing contrast agents. Most deaths occur during injection or 5 to 10 minutes later; the main feature being cardiac arrest with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. Based upon clinical literature, reported deaths from the administration of conventional iodinated contrast agents range from 6.6 per 1 million (0.00066 percent) to 1 in 10.000 patients (0.01 percent). Repardless of the contrast agent employed, the overall

range from 6.6 per 1 million (0.00066 percent) to 1 in 10.000 patients (0.01 percent). Regardless of the contrast agent employed, the overall estimated incidence of serious adverse reactions is higher with coronary arteriography than with other procedures. Cardiac decompensation, serious arrhythmias, or myo-cardial ischemia or inflarction may occur during coronary arteriography and left ventriculography.

The most frequent adverse reactions are nausea, vomiting, facial flush and a feeling of body warmth. These are usually of brief duration, in double-bind clinical trials, HEXABRIX produced less discomfort upon injection (pain and heat) when compared to various other contrast agents. Other reactions include the following:

Hypersensitivity reactions: Dermal manifestations of urticaria with or without prurflus, erythema and maculopapular rash. Dry mouth, Sweating, Conjunctival symptoms. Facial, peripheral and angioneurotic edema. Symptoms related to the respiratory system include sneezing, nasal stuffiness, couphing, choking, dyspnea, chest tightness and wheezing, which may be initial manifestations of more severe and infrequent reactions including asthmatic attack, laryngospasm and bronchospasm with or without deema, pulmonary edema, apnea and cyanosis. Rarely, these allergic-type dema. edema, apnea and cyanosis. Rarely, these allergic-type reactions can progress into anaphylaxis with loss of sciousness, coma, severe cardiovascular disturba

Cardiovascular reactions: Generalized vasodilation, flush Cardiovascular reactions: Generalized vasoditation, flushing and venospasm. Ocasionally thrombosis or, rarely, thrombophlebitis. Extremely rare cases of disseminated intravascular coagulation resulting in death have been reported. Severe cardiovascular responses include rare cases of hypotensive shock, coronary insufficiency, cardiac arrhythmia, fibrillation and arrest. These severe reactions are usually reversible with prompt and appropriate management; however, fatalities have occurred. Technique reactions: Extravasation with burning pain, hematomas, ecchymosis and tissue necrosis, vascular constriction due to injection rate, thrombosis and thrombophlebitis.

thrombophlebitis

Neurological reactions: Spasm, convulsions, aphasia, syncope, paresis, paralysis resulting from spinal cord injury and pathology associated with the syndrome of transverse myelitis, visual field losses which are usually transient but may be permanent, coma and death.

Other reactions: Headache, trembling, shaking, chilis without lever, hyperthermia and lightheadedness. Temporary renal shutdown or other nephropathy.
Pediatric angiocardiography has been complicated by intramural injection with marked adverse effects on cardiac function.

Internation injection with marked services clearly and charles function.

During selective coronary arteriography with or without left ventriculography, patients may have clinically insignificant EGG changes. The following adverse effects have occurred in conjunction with the administration of loindated intravascular contrast agents for this procedure: hypotension, shock, anginal pain, myocardial infarction, cardiac arrhythmias (bradycardia, ventricular tachycardia, ventricular fibrillation) and cardiac arrest. Fatalities have been reported. Complications to the procedure include dissection of coronary arteries, dislodgement of atheromatous plaques, perforation, hemorrhage and thrombosis. Following peripheral arteriography, hemorrhage and thrombosis have occurred at the puncture site of the percutaneous injection. Brachial plexus injury has been reported following axiliary artery injection.

lowing axillary artery injection.
The major causes of cerebral arteriographic adverse reac following axillary artery injection.

The major causes of cerebral arteriographic adverse reactions appear to be repeated injections of the contrast material, administration of doses higher than those recommended, the presence of occlusive atherosclerotic vascular disease and the method and technique of injection. Adverse reactions are normally mild and transient. A feeling of warmth in the face and neck is frequently experienced. Infrequently, a more severe burning discomfort is observed. Transient visual hallucinations have been reported. Serious neurological reactions that have been associated with cerebral angiography and not listed under Adverse Reactions include stroke, ammesia and respiratory difficulties. Visual field defects with anopsia and reversible neurological deficit lasting from 24 hours to 48 hours have been reported. Confusion, disorientation with hallucination, and absence of vision sometimes lasting for one week have also been reported. Cardiovascular reactions that may occur with some frequency are bradycardia and either an increase or decrease in systemic blood pressure. The blood pressure change is transient and usually requires no treatment. Arthrography may induce joint pain or discomfort which is usually mild and transient but occasionally may be severe and persist for 24 to 48 hours following the procedure. Effusion requiring aspiration may occur in patients with rheumatoid arthritis. Fever and pain, cramping and tenderness of the abdomen have been reported following hysterosalpingography. hysterosalpingography

#### **OVERDOSAGE**

OVERDOSAGE

Overdosages may occur. The adverse effects of overdosage are lite-threatening and affect mainly the pulmonary and cardiovascular systems. The symptoms may include cyanosis, bradycardia, acidosis, pulmonary hemorrhage, convulsions, coma and cardiac arrest. Treatment of an overdose is directed toward the support of all wital functions and prompt institution of symptomatic therapy.

Ioxaglate saits are dialyzable.

The intravenous LDgo values of HEXABRIX (in grams of iodine/kilogram body weight) were 11.2 gr/kg in mice, > 8 g/kg in rats, > 6.4 g/kg in rabbits and > 10.2 gr/kg in dogs.

#### DOSAGE AND ADMINISTRATION

Details on dosage are are provided in the packa SULT FULL PACKAGE INSERT BEFORE USE. Rev. Nov. 1989.

Rev. Nov. 1899.

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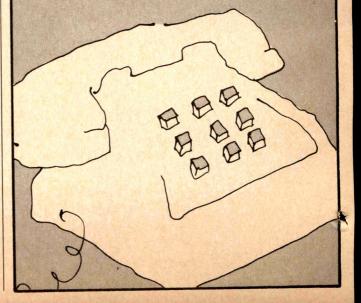
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# Usefulness of Silent Ischemia, Ventricular Tachycardia, and Complex Ventricular Arrhythmias in Predicting New Coronary Events in Elderly Patients with Coronary Artery Disease or Systemic Hypertension

Wilbert S. Aronow, MD, and Stanley Epstein, MD

Ventricular tachycardia (VT), complex ventricular arrhythmias and silent ischemia detected by 24-hour ambulatory electrocardiographic monitoring contribute to new coronary events in elderly patients with heart disease. 1-3 We performed a prospective study to find the correlation of VT, complex ventricular arrhythmias and silent ischemia to new cardiac events in patients over 62 years of age with coronary artery disease (CAD) or hypertension.

Patients in our long-term health care facility were considered to have CAD at entry into the study if they had a documented clinical history of myocardial infarction, electrocardiographic evidence of Q-wave myocardial infarction or angina pectoris. A systolic blood pressure of ≥160 mm Hg on 3 occasions was considered systolic hypertension and a diastolic blood pressure of ≥90 mm Hg on 3 occasions was considered diastolic hypertension. Blood pressure recordings were obtained at different times during the day.

Ambulatory electrocardiographic monitoring was performed for 24 hours using portable Avionics tape recorders (model 445) to obtain 2 leads corresponding to a modified  $V_1$  and  $V_5$ . The tapes were analyzed using a CardioData Mk 3 computer system. Rhythm disturbances and ST-segment changes were written out on electrocardiographic paper at a speed of 25 mm/s and interpreted by 2 cardiologists. Patients with marked resting ST-segment depression (≥1.5 mm) were excluded from the study. Silent ischemia was diagnosed if horizontal or downsloping ST-segment depression ≥1.0 mm below the resting level occurred at 80 ms after the J point, if it lasted for ≥1.0 minute and if it was unassociated with anginal symptoms. If resting ST-segment depression occurred, an additional 2.0 mm of ischemic STsegment depression below the resting level at 80 ms after the J point was required. In selected patients, similar ST-segment changes after treadmill exercise associated with angina were obtained. Ventricular premature complexes were graded according to Lown's4 classification. Ventricular tachycardia was defiend as ≥3 consecutive ventricular premature complexes.5 Complex ventricular arrhythmias included VT, or paired, multiform or frequent (≥30/hr) ventricular premature complexes.1,2

Technically satisfactory 24-hour ambulatory electrocardiographic recordings were obtained in 404 of 487 patients (83%). The 404 patients were made up of 293 women and 111 men with a mean age of  $82 \pm 8$  years (range 62 to 98). Two hundred thirty-six of these pa-

**TABLE I** Prevalence of Silent Ischemia, Ventricular Tachycardia and Complex Ventricular Arrhythmias in Elderly Patients with Coronary Artery Disease or Hypertension

	Silent Ische		VT		Com	plex
	No.	%	No.	%	No.	%
CAD with or without hypertension (236)	82	35	35	15	159	67
Hypertension without CAD (168)	28	17	13	8	75	45
CAD or hypertension (404)	110	27	48	12	234	58

**TABLE II** Correlation of Silent Ischemia to Ventricular Tachycardia and Complex Ventricular Arrhythmias in Elderly Patients with Coronary Artery Disease or Hypertension

No.	%	No.	%
24	22*	81	74*
24	8	153	52
	24	24 22*	24 22* 81

tients had CAD with or without systemic hypertension and 168 had systemic hypertension without CAD. Patients with VT or complex ventricular arrhythmias were treated with antiarrhythmic drugs. Patients with CAD and silent ischemia were treated with antiischemic drugs.

The mean follow-up period was  $37 \pm 10$  months (range 15 to 49). New cardiac events were diagnosed if the patient developed myocardial infarction, primary ventricular fibrillation or sudden cardiac death. Myocardial infarction was documented as previously described. Sudden cardiac death was defined as an unexpected cardiac death in a patient with systemic hypertension or CAD found dead within 1 hour of being clinically stable. Data on other cardiac events such as new onset angina, unstable angina or congestive heart failure are available but not reported since these cardiac events were not included in the original design of this prospective study. Chi-square analyses were used to analyze data.

At 37-month follow-up, new cardiac events occurred in 201 of 404 patients (50%). Table I lists the prevalence of silent ischemia, VT and complex ventricular arrhythmias in patients with CAD, hypertension without CAD, and CAD or hypertension. Table II lists the correlation of silent ischemia to VT and to complex ventricular

From Hebrew Hospital for Chronic Sick, 2200 Givan Avenue, Bronx, New York 10475. Manuscript received August 30, 1989; revised manuscript received and accepted October 11, 1989.

TABLE III Correlation of Silent Ischemia, Ventricular Tachycardia and Complex Ventricular Arrhythmias to New Cardiac Events in Elderly Patients with Coronary Artery Disease or Hypertension

	Cardiac Events	
	No.	%
Silent ischemia	87/110	79*
No silent ischemia	114/294	39
VT	37/48	77*
No VT	164/356	46
Complex VA	153/234	65*
No complex VA	48/170	28

**TABLE IV** Correlation of Silent Ischemia and Ventricular Tachycardia to New Cardiac Events in Elderly Patients with Coronary Artery Disease or Hypertension

<b>"这种是是是是是这种的。"</b>	Cardiac Event	s
	No.	%
A. No silent ischemia, no VT	99/270	37
B. Silent ischemia, no VT	65/86	76
C. VT, no silent ischemia	15/24	63
D. VT, silent ischemia	22/24	92

 $p<\!0.001$  when comparing D with A and B with A;  $p<\!0.02$  when comparing C with A and D with C. VT = ventricular tachycardia.

**TABLE V** Correlation of Silent Ischemia and Complex Ventricular Arrhythmias to New Cardiac Events in Elderly Patients with Coronary Artery Disease or Hypertension

<b>文学规则是是是对自己的</b>	Cardiac Ever	nts
	No.	%
A. No silent ischemia, no complex VA B. Silent ischemia, no complex VA C. Complex VA, no silent ischemia D. Complex VA, silent ischemia	29/141 19/29 85/153 68/81	21 66 56 84

 $p<\!0.001$  when comparing D with A, D with C, C with A and B with A;  $p<\!0.05$  when comparing D with B. VA = ventricular arrhythmias.

arrhythmias in patients with CAD or hypertension. Table III lists the correlation of silent ischemia, VT and complex ventricular arrhythmias to new cardiac events in patients with CAD or hypertension. Table IV lists the correlation of silent ischemia and VT to new cardiac events in patients with CAD or hypertension. Table V lists the correlation of silent ischemia and complex ventricular arrhythmias to new cardiac events in patients with CAD or hypertension.

Gottlieb et al<sup>8</sup> showed that 9 of 30 (30%) high-risk postinfarction patients with silent ischemia detected by ambulatory electrocardiographic monitoring were dead at 1 year compared to 8 of 73 patients (11%) without silent ischemia. In this study, ventricular arrhythmias were significantly more frequent during hours in which silent ischemia was detected. Nademanee et al<sup>9</sup> observed in a study of 41 patients with unstable angina that ventricular arrhythmias detected by ambulatory electrocar-

diographic monitoring were associated with 18% of ischemic episodes.

Several case reports have also shown an association between silent ischemia and arrhythmic sudden death.<sup>10-12</sup> Sharma et al<sup>13</sup> demonstrated exercise-induced silent ischemia in 12 of 15 patients (80%) with CAD who survived out-of-hospital ventricular fibrillation. Sharma and Wyeth<sup>14</sup> also showed that the 6-year survival rate of patients with and without silent ischemia and out-of-hospital ventricular fibrillation was similar.

Our data show that in elderly patients with CAD or systemic hypertension, the prevalence of VT and of complex ventricular arrhythmias at baseline was greater in patients with silent ischemia at baseline than in patients without ischemia at baseline. Our data also show that silent ischemia, VT and complex ventricular arrhythmias were each significantly associated with new cardiac events at a mean follow-up of  $37 \pm 10$  months. In patients with or without VT or complex ventricular arrhythmias, silent ischemia was associated with an increased incidence of new cardiac events. VT or complex ventricular arrhythmias were each associated with new cardiac events even in the absence of silent ischemia. Silent ischemia with complex ventricular arrhythmias was more likely to be associated with new cardiac events than silent ischemia without complex ventricular arrhythmias. However, whether or not the increased risk for new cardiac events was caused by silent ischemia provoking malignant ventricular arrhythmias is not clear from our study.

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#### **Left Main Coronary Artery Disease Progression After Percutaneous Transluminal Coronary Angioplasty**

Catherine M. Kells, MD, Robert M. Miller, MD, Mark A. Henderson, MD, Judy M. Lomnicki, RCPT, and Robert G. Macdonald, MD

Studies have evaluated the frequency of coronary artery disease progression after percutaneous transluminal coronary angioplasty (PTCA)1,2 and there have been many reports of isolated cases of new left main coronary artery (LMCA) stenosis or significant disease progression in the LMCA after PTCA of the left anterior descending or left circumflex arteries.3-6 The reports of LMCA disease progression have dealt only with patients in whom significant symptoms prompted repeat coronary angiography after initial PTCA. To date, there has been no systematic study of this finding to determine accurately the incidence of this potentially serious problem and whether it can be considered a direct complication of PTCA. This study determines the incidence of new stenosis or disease progression in the LMCA after successful PTCA and attempts to determine whether the occurrence of LMCA disease progression may be directly attributable to a preceding PTCA procedure.

The study represents a retrospective angiographic analysis of a consecutive series of patients who had PTCA between July 1986 and December 1987. All patients underwent PTCA in the usual fashion using conventional "over the wire" catheter systems (USCI). Medications were aspirin 325 mg once daily and standard antianginal therapy. Heparin (10,000 U), given intravenously at the start of the procedure, was supplemented in longer procedures and continued after PTCA only in cases where significant dissection occurred.

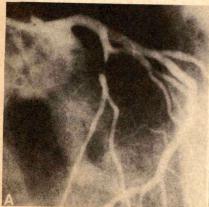
From the Division of Cardiology, Department of Medicine, Dalhousie University, Halifax, and the Victoria General Hospital, Room 3042, Halifax, Nova Scotia, Canada B3H 2Y9. This study was supported in part by the Nova Scotia Branch of the Canadian Heart Foundation. Manuscript received August 16, 1989; revised manuscript received and accepted October 16, 1989.

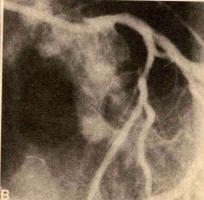
In conjunction with an ongoing restenosis study at our institution, follow-up coronary angiography with repetition of original angiographic views was routinely scheduled in all patients at 6 months after successful PTCA unless a contraindication existed or the patient refused. Earlier angiography was performed for symptom recurrence. Paired angiograms (before PTCA and follow-up) were selected for comparison. During analysis of the angiograms we noted which artery was dilated. We also noted whether balloon dilation partially involved the LMCA or resulted in dissection of the LMCA in cases involving proximal left anterior descending or left circumflex stenoses.

Angiograms were projected at 2- to 3-fold magnification and measured using handheld calipers and a ruler. LMCA absolute diameter and percent stenosis were obtained from the initial and follow-up angiograms using comparable angiographic views. The proximal, midand distal LMCA was measured. Percent stenosis was expressed to the nearest 5%. Each case was reviewed independently by at least 2 experienced angiographers.

Successful PTCA was defined as <50% residual diameter stenosis without significant complications. Detectable LMCA narrowing was considered >20% stenosis. Disease progression was defined as an increase in stenosis by >20% when comparing the follow-up angiogram to that obtained immediately before PTCA.

For the purpose of this study, 2 patient groups were established to separate cases in which the balloon catheter crossed through the LMCA from those in which the left coronary artery was not instrumented other than by a diagnostic catheter. Group I included patients who had PTCA in the left coronary artery system and group II included patients who had PTCA in vessels such as the





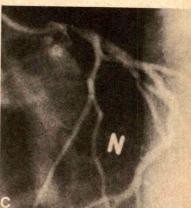


FIGURE 1. A, left anterior oblique cranial view of the left coronary artery before percutaneous transluminal coronary angioplasty (PTCA). The left anterior descending artery has a severe proximal stenosis and the left main coronary artery (LMCA) shows no significant narrowing. B, angiogram performed after PTCA demonstrating patency of the left anterior descending artery and minimal ostial narrowing of the LMCA. C, angiogram performed 8 months after PTCA for symptom recurrence shows an 80% ostial stenosis of the LMCA and continued patency of the left anterior descending artery. Coronary artery bypass surgery was performed.

right coronary artery or bypass grafts. The incidence of new disease or disease progression after successful PTCA was then compared in the 2 groups. Differences between the 2 groups were analyzed using the chi-square test. A p value <0.05 was considered significant.

There were 426 patients who had successful PTCA procedures from July 1986 to December 1987. Of these, 381 had angiographic restudy (89% follow-up) at a mean of 6.8 months after PTCA. Eighty-eight pairs of angiograms were excluded because of a short LMCA (<5 mm length) or anomalous origin of the circumflex artery such that the LMCA could not be reliably measured or was nonexistent. Thus, there were 293 pairs of angiograms for final analysis. Of these, 230 had PTCA in the left coronary artery (group I) and 63 had PTCA in another artery (group II). Before PTCA there were 24 cases of detectable LMCA narrowing in group I (10.4%) and 6 cases in group II (9.5%, difference not significant). At follow-up, there were 4 cases of LMCA disease progression and these were limited to the group that had PTCA in the left coronary artery and to patients with detectable narrowing in the LMCA before PTCA. Therefore, the incidence of disease progression was 17% in group I versus 0% in group II (difference not significant). In considering the total population (with or without preexisting LMCA disease), the incidence of either new LMCA disease or disease progression was 4 of 230 group I patients (1.7%) versus 0 of 63 group II patients (difference not significant). The overall incidence of significant LMCA disease progression for all patients analyzed (groups I and II combined) was 4 of 293 (1.3%).

Although the PTCA balloon was inflated partially in the LMCA in 2 of the 4 cases, there was no evidence in any case of LMCA dissection either by balloon inflation or guide catheter manipulation. All 4 cases had disease progression in the distal LMCA, but as shown in Figure I from a case occurring after completion of this study, disease progression may occur in proximal segments as well. Significant disease progression in other arterial segments did not occur in any of the 4 patients who had LMCA disease progression after PTCA although restenosis of the dilated artery occurred in 3 cases. Of the 4 cases of disease progression, 2 were after PTCA in the circumflex artery (from 35 to 60% and 30 to 65%) and 2 in the left anterior descending artery (from 20 to 40% and 40 to 80%). Three patients required coronary bypass surgery, 1 on an urgent basis and 2 on an elective basis. No patient either had a myocardial infarction or died as a result of LMCA disease progression.

Development of significant LMCA disease after PTCA is infrequent, occurring in only 1.7% of patients who had PTCA involving the left coronary artery and none of the patients with PTCA in other vessels in this

series. The finding that only group I patients developed disease progression might suggest this phenomenon is directly related to the procedure in the left coronary artery. There were, however, not enough cases for us to evaluate such an association. With such a low incidence of disease progression, a study of >1,500 patients would be necessary to address this question properly. The data do suggest that patients with measurable LMCA stenosis before PTCA may be at increased risk of subsequent disease progression compared to patients without obvious LMCA disease (17 vs 0%, p <0.001).

This study is the first to evaluate systematically the incidence of LMCA disease progression in a large series of patients with a high degree of angiographic follow-up (89%) and provides evidence that the incidence of LMCA disease progression early after PTCA is low. Studies in animal models have used catheter denudation of arterial endothelium to accelerate development of atherosclerosis after administration of an atherogenic diet. It seems reasonable to assume that balloon catheter transit through proximal coronary segments might cause accelerated atherosclerosis or increased fibrocellular proliferation in humans, particularly at the distal LMCA where abrupt tapering and branching occurs. Our data show this is an infrequent phenomenon, at least in the short term, and failed to demonstrate an association with the procedure. Ideally, follow-up angiography should be performed again, at least 3 years after PTCA, to assess later development of significant LMCA narrowing or disease progression at other sites. Obviously, this would be hard to justify on a routine basis in a large number of patients.

In conclusion, patients undergoing PTCA are at low risk of developing progression of disease in the LMCA after an initially successful procedure. Whether this phenomenon is a true complication of the procedure can only be answered by a much larger scale study. Based on our current experience, we do not consider this potential complication of PTCA to be of major clinical importance.

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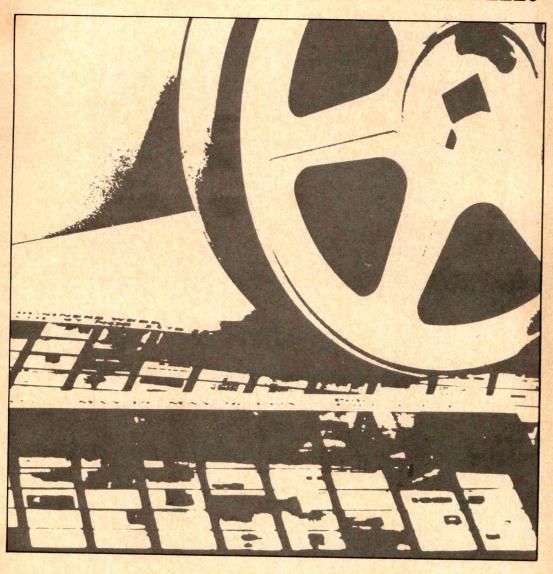
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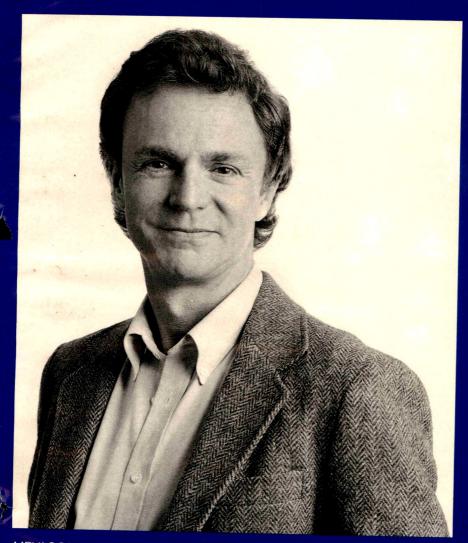
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# Who's getting results on MEVACOR®?

(LOVASTATIN | MSD)



MEVACOR is indicated as an adjunct to diet for the reduction of elevated total and LDL cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when response to nonpharmacologic measures has been inadequate.

MEVACOR is contraindicated in patients who are hypersensitive to any component of the medication; in patients with active liver disease or unexplained persistent transaminase elevations; in pregnant or lactating patients; and in women of childbearing age, except when such patients are highly unlikely to conceive.

It is recommended that liver function tests be performed before treatment begins, every 4 to 6 weeks during the first 15 months of therapy, and periodically thereafter in all patients.

The effect of lovastatin-induced changes in serum lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity or mortality has not been established.

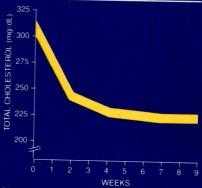
For more details on warnings, precautions, and adverse reactions, including cautionary information regarding liver dysfunction, myopathy, and slit-lamp monitoring, please see Prescribing Information.

For a Brief Summary of Prescribing Information, please see the following page.

#### Patient J.D.

- Male, age 42, asymptomatic for cardiac disease
- Father and paternal uncle died of premature coronary heart disease
- Elevated total cholesterol of 305 mg/dL after adequate trial of a cholesterol-lowering diet
- After 7 weeks on
   MEVACOR, total
   cholesterol is 223 mg/dL
   (dosage: 20 mg b.i.d.)

#### **Results with MEVACOR**



Not everyone will respond as did the patient in this hypothetical case history; however, the mean reduction in total cholesterol in clinical trials was 17% at 20 mg once a day and 27% at 20 mg b.i.d.







Now available as a 40-mg tablet

ONTRAINDICATIONS: Hypersensitivity to any component of this

liver disease or unexplained persistent elevations of serum

Pregnancy and lactation.

Atherosclerosis is a chronic process and the discontinuation of lipidowering drugs during pregnancy should have little impact on the outcome
of long-term therapy of primary hypercholesterolemia. Moreover, choleserol and other products of the cholesterol biosynthesis pathway are esential components for fetal development, including synthesis of steroids
and cell membranes. Because of the ability of inhibitors of HMG-CoA retilctaes such as MEVACOR\* (Lovastain, MSD) to decrease the synthesis
of cholesterol and possibly other products of the cholesterol biosynthesis
oathway. MEVACOR may cause fetal harm when administered to a pregnant woman. Therefore, lovastatin is contraindicated during pregnancy.
Lovastatin should be administered to women of childbearing age only
when such patients are highly unlikely to conceive. If the patient becomes
pregnant while taking this drug, lovastatin should be discontinued and the
patient should be apprised of the potential hazard to the fetus.

VARNINGS: Liver Dystunction: Marked persistent increases (to more han 3 times the upper limit of normal) in serum transaminases (curred in 19% of adult patients who received lovastatin for at least me year in clinical trials (see ADVERSE REACTIONS). When the drug was the patients who transaminase lower to the patients that transaminase lower to the patients that transaminase lower to the patients who there are the patients who the patients who there are the patients who the patients who there are the patients who the patients who there are the patients who the patients who there are the patients who the patients who there are the patients who there are the patients where the patients who occurred in 1.9% of adult patients who received trovastain at least mey are inlined trials (see ADVERSE REACTIONS). When the drug was interrupted or discontinued in these patients, the transaminase levels usually yell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. A liver biopsy was done in one of these patients and showed areas of local hepatitis. In this patient, transaminase levels returned to normal following discontinuation of therapy. Some of these patients had abnormal liver function tests prior to lovastatin therapy and/or consumed substantial quantities of alcohol.

It is recommended that liver function tests be performed before treatment begins, every 4 to 6 weeks during the first 15 months of therapy with lovastatin, and periodically thereafter in all patients. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations are persistent beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms, and interruption of treatment was not required.

These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms, and interruption of treatment was not required.

Skeletal Muscle: Several cases of rhabdomyolysis have been associated with lovastatin therapy alone, when combined with immunosuppressive therapy including cyclosporine in cardiac transplant patients, and when combined in non-transplant patients with either gemtibrozil or lipid-lowering doses (≥ 1 g/day) of nicotinic acid. Acute renal failure from rhabdomyolysis has been seen more commonly with the lovastatin-gemtibrozil combination and has also been reported in transplant patients receiving lovastatin plus cyclosporine.

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving crythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored.

Fulminant rhabdomyolysis has been seen as early as 3 weeks after initiation of combined therapy with gemtibrozil and lovastatin but may be seen after several months. For these reasons, it is felt that in most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefits of combined therapy with lovastatin and gemtibrozil do not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemtibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of lovastatin with other fibrates shoul deerally be avoided.

Physicians contemplating combined therapy with lovastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should acrefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of the

including in accomplinate by imbasics on two. New Jonathy is diagnosed or suspected.

Most of the patients who have developed myopathy (including rhabdomyolysis) while taking lovastatin were receiving concomitant therapy with immunosuppressive drugs, gentfibrozil, or lipid-lowering doses of nicotinic acid. In clinical trials, about 30% of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy, the corresponding percentages for gemtibrozil and niacin were approximately 5% and 2%, respectively.

In 6 patients with cardiac transplants taking immunosuppressive therapy including cyclosporine concomitantly with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately 4 times the expected levels. Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered.

PRECAUTIONS: General: Before instituting therapy with MEVACOR® (Lovastatin, MSD), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in obese patients and to treat other underlying medical problems (see INDICATIONS AND

USAIGE).
Lovastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

ential diagnosis of chest pain in a patient on therapy with lovastatin.

Eye: There was a high prevalence of baseline lenticular opacities in the patient population included in the clinical trials with lovastatin. During these trials the appearance of new opacities was noted. The causal relationship of lovastatin to these findings has not been established. Of 431 patients examined with silt lamp at baseline and during therapy with lovastatin, 34 had opacities reported at the final examination (5 to 15 months after starting lovastatin) that were not noted at baseline were not noted at the final examination, so that the prevalence did not increase. There was no clinically significant change in visual acutly in the patients who had new opacities reported, nor was any patient, including those with opacities noted at baseline, discontinued from therapy because of a decrease in visual acutly. Nevertheless, until further experience is obtained, it is recommended that patients placed on lovastatin therapy be examined with a slit lamp before or shortly after initiation of treatment and annually thereafter.

Homozygous Familial Hypercholesterolemia: MEVACOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

\*\*Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See WARNINGS, Skeletal Muscle. Coumarin Anticoagulants: In a clinical trial in warfarin-treated patients designed specifically to observe a potential effect of lovastatin on the prothrombin time, lovastatin in dosages up to 40 mg b.i.d. did not produce any consistent atteration of the anticoagulant action of warfarin. However, since the drug was marketed, clinically evident bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants: concomitantly with lovastatin. The causal relationship to lovastatin is unclear. Nevertheless, it is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants. \*Antipyrine: Antipyrine is a model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P450 system). Because lovastatin had no effect on the pharmacokinetics of antipyrine, interactions with other drugs metabolized via this mechanism are not expected. \*Propranolof: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacokynamic interaction with concomitant administration of single doses of lovastatin and propranolol. \*Digoxin: In patients with hypercholesterolemia, concomitant administration. \*Direct Concomitant Interaction to reflect on studies were not performed in directions.

concentrations.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, lovastatin was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 21-month carcinogenic study in mice, a statistically significant (p<0.05) increase in the incidence of hepatocellular carcinomas and adenomas was observed at doses of 500 mg/kg/day (312 times the maximum recommended human dose) of lovastatin. These changes were not seen in mice given doses of 20 and 100 mg/kg/day (12.5 and 62.5 times the maximum recommended human dose). nded human dose)

ommended human dose).

A statistically significant increase (p≤0.05) in the incidence of pulmonary adenomas was seen in female mice receiving 500 mg/kg/day (312 times the maximum recommended human dose); no similar chapter were seen in males at any dose or in females receiving 20 or 100 mg/kg/day (12.5 or 62.5 times the maximum recommended human dose). Because the incidence of pulmonary tumors was within the range of untreated animals in studies of similar duration, the relationship of this

cause the incidence of pulmonary tumors was within time range of untreated animals in studies of similar duration, the relationship of this latter change to treatment is not known. In addition, an increase in the incidence of papilloma in the non-glandular mucosa of the stomach was observed in mice receiving 100 and 500 mg/kg/day (62.5 and 312 times the maximum recommended human dose); no increase was seen at a dosage of 20 mg/kg/day (12.5 times the maximum recommended human dose). The glandular mucosa was not affected. The human stomach contains only glandular mucosa importantly, there is a strong association between this change and hyperplasis of the squamous epithelium (acanthosis) in this region; acanthosis is a characteristic change observed in the non-glandular mucosa of rodents treated with HMG-CoA reductase inhibitors and is most probably a result of inhibition of the reductase inhibitors and is most probably a result of inhibition of the mouse apithelium is found in the esophagus and anorectal junction of the mouse and rat; however, no evidence of a similar drug-induced hyperplastic response was observed in these tissues is studies of up to 21 months in the mouse given up to 500 mg/kg/day (312 times the maximum recommended human dose), or in a study of 24 months in the ratification and the study of 24 months in the mouse given up to 500 mg/kg/day (312 times the maximum recommended human dose).

dose). In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for hepatocellular carcinogenicity in males (unadiusted p=0.025). However, because the incidence of hepatocellular carcinogenicity observed in male rats in this study is similar to that observed spontaneously in this strain of rat, the implications of this finding are unclear

unclear.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of Salmonella typhimurium with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an in vitro alkaline elution assay using rat or mouse hepatocytes. a V-79 mammalian cell forward mutation study, an in vitro chromosome aberration study in CHO cells, or an in vivo chromosomal aberration assay in mouse bone marrow.

No drug-related effects on fertility were found in studies with rats.

No drug-related effects on fertility were found in studies with ratio.

\*\*Pregnancy:\* Pregnancy Category X: See CONTRAINDICATIONS.

Lovastatin has been shown to produce skeletal malformations in the rat fetus at doses of 800 mg/kg/day (500 times the maximum recommended human dose). At similar doses in mice, an increase in skeletal malfordations was observed. These individual changes are within the range of those observed spontaneously in this strain of mouse. No drug-induced changes were seen in either species at doses of up to 80 mg/kg/day (50 times the maximum recommended human dose). No evidence of malformations was noted in rabbits at up to 15 mg/kg/day (ipplest tolerated one—about 9 times the maximum recommended human dose). There are no

Nursing Mothers: Studies in rats have shown that lovastatin is excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MEVACOR, women taking lovastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children have not been estab-lished. Because children are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no

studies in subjects below the age of 20 years), treatment of children with lovastatin is not recommended at this time.

ADVERSE REACTIONS: MEVACOR® (Lovastatin, MSD) is generally well tolerated; adverse reactions usually have been mild and transient. Less than 1% of patients were discontinued from controlled clinical studies due to adverse experiences attributable to MEVACOR. About 2% of patients were discontinued from all studies (controlled and uncontrolled) di adverse experiences attributable to MEVACOR; about one-third of t patients were discontinued due to increases in serum transaminases

Clinical Adverse Experiences: Adverse experiences reported in patients treated with MEVACOR in controlled clinical studies are shown in the table

	MEVACOR (N = 613)	Placebo (N = 82) %	Cholestyramine (N = 88) %	Probucol (N = 97) %
Gastrointestinal			04.4	0.1
Constipation	4.9	_	34.1	2.1
Diarrhea	5.5	4.9	8.0	10.3
Dyspepsia	3.9		13.6	
Flatus	6.4	2.4	21.6	2.1
Abdominal pain/cramps	5.7	2.4	5.7	5.2
Heartburn	1.6	_	8.0	
Nausea	4.7	3.7	9.1	6.2
Musculoskeletal				
Muscle cramps	1.1	_	1.1	_
Myalgia	2.4	1.2	_	_
Nervous System/Psychiatric	;			
Dizziness	2.0	1.2	_	1.0
Headache	9.3	4.9	4.5	8.2
Skin				
Rash/pruritus	5.2	_	4.5	_
Special Senses				0.4
Blurred vision	1.5	_	1.1	3.1
Dysgeusia	0.8		1.1	_

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase (CPK) levels of at least twice the normal value on one or more occasions. The corresponding values for the control agents were cholestyramine, 9% and probucol, 2%. This was attributable to the noncardiac fraction of CPK. Large increases in CPK have sometimes been reported (see WARNINGS, Skeletal Muscle).

Concomitant Therapy: In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with immunosuppressive drugs, gemtibrozil, or niacin (nicotinic acid) (see WARNINGS, Skeletal Muscle).

Uncontrolled Clinical Studies: The adverse experiences observed in Uncontrolled Linical Studies: The adverse experiences observed if uncontrolled studies were similar to those seen in controlled clinical studies. Abnormal liver function tests were observed at a higher incidence than in the controlled studies (see WARNINGS, Liver Dysfunction). Myopathy (myalgia with marked CPK elevations) was reported in approximately 0.5% of patients (see WARNINGS, Skeletal Muscle).

Causal Relationship Unclear: Nervous System: Peripheral neuropathy has been reported; the relationship to lovastatin is uncertain. Visual evoked response, nerve conduction measurements, and electromyography in over 30 patients showed no evidence of neurotoxic effects of

ovastatin. Special Senses: 01 431 patients examined with slit lamp at baseline and during therapy with lovastatin, 34 had opacities reported at the final examination (5 to 15 months after starting lovastatin) that were not noted at baseline. On the other hand, in 45 patients, opacities observed at baseline were not noted at the final examination, so that the prevalence did not increase (see PRECAUTIONS).

Post-marketing Experience: Additional adverse experiences occurring since the drug was marketed are listed below: Clinical Adverse Experiences Gastrointestinal: Hepatitis, cholestatic jaundice, anorexia,

vomiting. Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus-like syndrome, polymyalgia rheumatica, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensi-

tivity, fever, and malaise.

Nervous System/Psychiatric: Psychic disturbances, including anxiety: paresthesia.
Causal Relationship Unknown
Gastrointestinal: Pancreatitis, stomatitis.
Skin: Alopecia.
Svetem/Psychiatric: Depression

Nervous System/Psychiatric: Depression, insomnia

Metabolic: Edema.
Clinical Laboratory Test Findings
Liver Function Tests: Liver function test abnormalities, including elevated alkaline phosphatase and bilirubin.

elevated alkaline phosphatase and bilirubin. **OVERDOSADE:** The oral LD<sub>50</sub> of MEVACOR in mice is 20 g/kg.

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported; no patients had specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 52 20-mg tablets (1.04 g).

Until further experience is obtained, no specific treatment of overdosage with MEVACOR can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION: The patient should be placed on a standard cholesterol-lowering diet before receiving MEVACOR and should continue on this diet during treatment with MEVACOR. MEVACOR should

continue of this use turning treatment without the given with meals.

The recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 20 to 80 mg/day in single or divided doses; the maximum recommended dose is 80 mg/day. Adjustments of dosage should be made at intervals of 4 weeks or more. Doses should be individualized according to the patient's response (see Tables I to IV under CLINICAL PHARMACOLOGY, Clinical Studies for dose

response results).
For those patients with severely elevated serum cholesterol levels
for those patients with severely elevated serum cholesterol levels
(i.e., >300 mg/dL [7.8 mmol/L] on diet), MEVACOR may be initiated at 40

mg/day.

In patients taking immunosuppressive drugs concomitantly with lovastatin (see WARNINGS, Skeletal Muscle), the maximum recommended dosage is 20 mg/day.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of MEVACOR if cholesterol levels fall below the targeted range.

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For more detailed information, consult your MSD Representative or see Prescribing Information, Merck Sharp & Dohme, Division of Merck & Co., INc., West Point, PA 19486. J8MC30R(508)

### Differential Hemodynamic Effects of Oral Enoximone in Severe Congestive Heart Failure

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Since impaired myocardial contractility is the primary deficit in a large number of patients with congestive heart failure (CHF), long-term treatment with oral positive inotropic agents has generated considerable interest over the last decade. A number of inotropic agents demonstrate salutary hemodynamic effects when administered short-term. Benefits of long-term therapy are, however, unclear. 2,3 The dose of the inotropic agent may be crucial to its overall efficacy since serious side effects and even death may occur at high doses.4 In a wide range of doses, both intravenous and oral forms of enoximone (an experimental phosphodiesterase inhibitor) exert positive inotropic, chronotropic and vasodilator effects in chronic CHF patients. 5,6 It has been shown that there is a plateau in the dose-effect relation of oral enoximone since doses in excess of 3.0 mg/kg do not offer any further hemodynamic benefit.7 Additionally, doses in the 3 to 6 mg/kg range appear to have a very high incidence of adverse side effects.8 The optimal dose of oral enoximone in chronic CHF is unknown. To determine whether the desirable and undesirable hemodynamic effects of oral enoximone are seen at different doses, we studied the short-term effects of various single doses (0.5 to 3.0 mg/ kg) of this drug in 65 patients with severe CHF.

Using a protocol and informed consent that was approved by our Institutional Review Board for Biomedical Research, we studied patients with severe CHF refractory to conventional therapy with digoxin, diuretics and vasodilators (including converting-enzyme inhibitors). All patients had a cardiothoracic ratio >50% on chest x-ray. The patient characteristics in each group are listed in Table I. Patients were excluded for: systolic blood pressure <85 mm Hg; uncontrolled ventricular arrhythmias; CHF secondary to hypertrophic or restrictive cardiomyopathy or valvular stenosis; child-bearing potential; and presence of primary hematologic, neurologic, renal or hepatic disease. Digoxin and diuretics were withheld on the study day. Vasodilator drugs were discontinued for at least 18 hours before hemodynamic measurements. Right-sided cardiac pressures and cardiac output were measured using a triple-lumen Swan-Ganz thermodilution catheter. Arterial pressure was measured directly. Cardiac output was determined in triplicate and the results were averaged. Arteriovenous oxygen difference was calculated from paired samples of systemic and pulmonary arterial blood.

patients at baseline and 4 hours after a single dose of enoximone are listed in Table II. Baseline hemodynamic variables were comparable in the various groups. Cardiac index and left ventricular stroke work index increased and systemic vascular resistance decreased significantly with all doses. The other hemodynamic effects were, however, apparent at different dose levels. The filling pressures significantly decreased only with 2.0 and 3.0 mg/kg doses; the heart rate increased significantly with all doses except 0.5 mg/kg and only the highest dose (3.0 mg/kg) caused the mean systemic arterial pressure to decrease significantly. The plasma norepinephrine level decreased significantly with the 2.0 mg/kg dose of enoximone and the plasma-renin activity increased signifi-

cantly after administration of 1.0 and 1.5 mg/kg doses.

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Supine baseline pressures, cardiac output and arteriovenous oxygen difference were measured twice, 15 minutes apart. Baseline data represent the average of these 2 sets of measurements. Venous blood samples for measuring baseline plasma norepinephrine level and plasma-renin activity were obtained immediately before drug dosing and after at least 60 minutes in the supine position. High-performance liquid chromatography was used to measure norepinephrine levels9 and a previously described radioimmunoassay technique was used to measure plasma-renin activity.10 Each patient was then given a single dose of oral enoximone. Group 1 patients (n = 12) received 0.5 mg/kg, group 2 patients (n = 24)1.0 mg/kg, group 3 patients (n = 8) 1.5 mg/kg, group 4 patients (n = 13) 2.0 mg/kg and group 5 patients (n = 8)were given 3.0 mg/kg. The initial patients received 3.0 mg/kg of oral enoximone. When information became available that lower doses of oral enoximone (<3.0 mg/kg) also improve hemodynamics in CHF (unpublished data from Merrell Dow Laboratories), the effects of decremental doses (2.0, 1.5, 1.0 and 0.5 mg/kg) were studied in consecutive groups of CHF patients. Repeat hemodynamic measurements and venous blood samples for plasma norepinephrine levels and renin activity were obtained 4 hours after drug dosing based on the expected peak effect as observed in previous studies.6 Derived hemodynamic measures (systemic vascular resistance, pulmonary vascular resistance and left ventricular stroke work index) were calculated using standard formulas. Baseline and postdrug hemodynamic data in each group were compared using the Student's t test for paired data. Kruskal-Wallis 1-way analysis of variance was used for comparisons among the different patient groups. Comparison of hormonal responses used the Wilcoxon sign-rank test. Statistical difference was defined as a p value <0.05. Hemodynamic and hormonal data for the 5 groups of

LE I Characteristics	Group 1	Group 2	Group 3	Group 4	Group 5
		24	8	13	8
No. of pts	12		1.5	2.0	3.0
Enoximone	0.5	1.0			
dose (mg/kg)		60 . 10	65 ± 10	61 ± 11	58 ± 7
Age (yrs)	59 ± 8	$60 \pm 12$	The second secon	9/4	6/2
Sex: M/F	7/5	18/6	6/2		2/6
NYHA III/IV	6/6	7/17	5/3	5/8	3/5
IDC/CAD	5/7	13/11	3/5	6/7	19±3
EF (%)	19±8	16 ± 6	20 ± 5	19 ± 7	19 ± 3

The magnitude of change from baseline in the various hemodynamic and hormonal parameters following administration of different doses of enoximone is shown in Figure 1. The heart rate, cardiac index, stroke volume index and stroke work index increased in a dose-dependent manner with increasing doses of enoximone. Likewise, a dose-related decrease was observed in the mean systemic arterial, right atrial and pulmonary artery wedge pressures, arteriovenous oxygen difference and systemic and pulmonary vascular resistances with increasing doses. Hemodynamic change from baseline was significantly greater with a 3.0 mg/kg dose of enoximone compared to lower doses. The heart rate increased to a greater extent with a 3.0 mg/kg dose compared to a 0.5 mg/kg dose. The change from baseline in cardiac index, stroke volume index and stroke work index with 3.0 mg/ kg of enoximone significantly exceeded that seen with 0.5 and 1.0 mg/kg doses. A significantly larger decrease in mean systemic arterial, right atrial and pulmonary artery wedge pressures, and systemic vascular resistance occurred with the 3.0 mg/kg dose compared to doses of 0.5, 1.0 and 1.5 mg/kg. The arteriovenous oxygen difference and pulmonary vascular resistance decreased to a greater extent with a 3.0 mg/kg dose compared to the other doses. Following administration of 0.5 and 1.0 mg/ kg of enoximone the plasma norepinephrine level tended to rise, but decreased with the other doses in a somewhat dose-dependent manner. Lower doses (0.5, 1.0 and 1.5 mg/kg) increased plasma-renin activity but other doses showed no significant change from baseline.

The results of our study indicate that in patients with severe CHF the degree of hemodynamic improvement with oral enoximone at doses ranging from 0.5 to 3.0 mg/ kg is, to a large extent, dose-related. A dose-response relation for both the magnitude and duration of hemodynamic improvement has been previously shown for the intravenous form of enoximone. 5,11 With oral enoximone, however, the hemodynamic effects reach a plateau at a dose of 3.0 mg/kg accompanied by a concomitant plateau in the plasma concentration of the drug.7 Previous studies have compared the short-term hemodynamic effects of different doses of oral enoximone. Gilbert et al12 administered varying doses of oral enoximone (≤2 mg/ kg) to 14 male patients with moderately severe CHF and noted a trend toward a dose-response relation both at 4 hours and 48 hours after drug administration. However, no significant differences were observed in the magnitude

of improvement between the low-dose (mean dose 0.98 ± 0.16 mg/kg) and high-dose (mean dose  $1.93 \pm 0.10 \text{ mg/mg}$ kg) groups. Jessup et al13 gave 12 patients with severe CHF 1.0 mg/kg of oral enoximone and demonstrated short-term improvement in cardiac performance. They also saw no significant difference in the magnitude of hemodynamic change in a subgroup of 6 patients who received both 1.0 and 2.0 mg/kg doses on successive days. The present study uses a much broader dose range (0.5 to 3.0 mg/kg) than the previous studies. As is apparent from Figure 1, a dose-dependent relation in the hemodynamic effects was observed. The magnitude of hemodynamic change among the different enoximone doses was different. Statistically significant differences were, however, present only between the 3.0 mg/kg dose of enoximone and the lower doses. This may be because of a large variability in response within each dosage group. Furthermore, the different hemodynamic effects became apparent at different dose levels.

In severe CHF, plasma norepinephrine levels and renin activity are frequently elevated.14 These hormones may be responsible for the activation of mechanisms that further compromise cardiac performance. In a previous study, we noted that larger doses of enoximone tended to increase plasma-renin activity but no change in norepinephrine levels was observed.8 It was hypothesized that the decrease in systemic blood pressure with a resultant decline in renal perfusion pressure was the stimulus for renin secretion. In the present study, the hormonal responses varied with different doses of enoximone. Lower doses (≤1.0 mg/kg) tended to increase norepinephrine levels whereas higher doses tended to decrease these levels in a dose-related manner. The response of plasmarenin activity was also varied such that lower doses (≤1.5 mg/kg) increased renin while higher doses caused no change despite a greater reduction in the mean arterial pressure. The reason for differences from our previous study is not apparent from the variables measured. If these hormonal data are representative of the effects of enoximone at different doses, they suggest a stimulation of renin release and activation of the sympathetic nervous system at lower doses, with less of an effect or a more balanced effect at higher doses. It should be emphasized that a heterogeneity of hormonal responses was present at all doses. No side effects were noted during the first dose administration of any of the doses of oral enoximone in this study. Previous studies have suggested a greater inci-

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14.9±6.1	15.1 ± 5.2	17.2±10.8*	12.6 ± 6.6	22.9±14.6*	18.6 ± 11.6	13.4 ± 8.4	10.8 ± 7.9
771 ± 304*	966 ± 359	726 ± 172	826 ± 198	980 ± 633	954 ± 628	824 ± 430	/30±380
20 ± 7*	16±5	21 ± 8*	19±5	17 ± 6*	15±5	15±4*	750 L 200
241 ± 107*	293 ± 155	244 ± 125	278 ± 93	291 ± 135	320 ± 137	2	284 ± 135
1,391 ± 279*	1,773 ± 467 1,	1,084 ± 356*	1,366 ± 127	1,529 ± 346†	1,738 ± 457	_	1,001 ± 300
6.1 ± 1.4†	7.8 ± 1.6	5.7 ± 1.4*	7.3 ± 1.9	7.1 ± 1.7 <sup>†</sup>	7.9 ± 1.8		1 901 + 507
25 ± 7*	21 ± 7	29 ± 9*	25 ± 4	22±7*	20 ± 5	22±6	75 - 15
2.4 ± 0.6 <sup>†</sup>	1.9 ± 0.5	2.8 ± 0.8*	2.2 ± 0.4	2.2 ± 0.5†	1.9 ± 0.4	2.1 ± 0.6	20 1 5
16±7*	23 ± 6	16±7	19±7	20 ± 8	22±7	21 ± 4	10 H 3
28 ± 10	34 ± 9	32±5	33 ± 6	34 ± 10	35 ± 8	32 ± /	) L L L L
4±6*	7±6	6±4	8±6	7±6	8±6	6 ± 4	2/ H H H H H H
<b>75±6</b>	79±8	73±7	75 ± 11	77±8	77 ± 7	/3±6	77.4
97 ± 16*	93±18	95 ± 15*	90 ± 14	103 ± 18†	90 ± 16		7 - 7
E	В	E	В	Е	B	E 97±10	95+14
	Group 4 (2.0 mg/kg)		Group 3 (1.5 mg/kg)		Group 2 (1.0 mg/kg)		(0.5 mg/kg)

dence of serious adverse effects with higher doses of enoximone when compared to lower doses.<sup>8,13</sup>

Based on these data, we would consider 0.5 to 1.0 mg/kg as a reasonable starting dose of enoximone, particularly if an increase in cardiac output signifies the possibility

of a salutary clinical response. In previous studies, however, acute hemodynamic responses, including changes in cardiac output, have been notoriously incorrect in predicting clinical improvement.<sup>7,15</sup> If significant decreases in filling pressures are necessary for clinical improve-

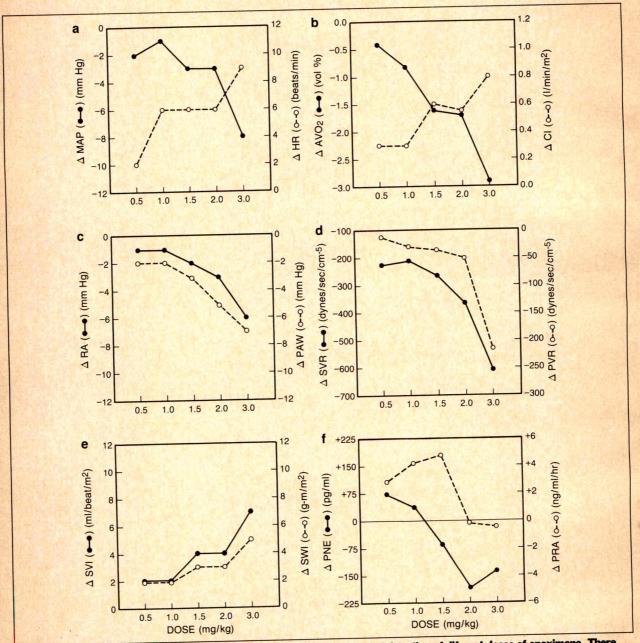


FIGURE 1. The magnitude of hemodynamic and hormonal change after administration of diferent doses of enoximone. There appeared to be a dose-dependent change in all the hemodynamic parameters (see also Table I); hormonal responses were heterogenous. A, the increase in heart rate (HR) was significantly greater with 3.0 mg/kg dose compared to 0.5 mg/kg. The mean arterial pressure (MAP) decreased to a larger extent with 3.0 mg/kg compared to 0.5, 1.0 and 1.5 mg/kg doses. B, the change from baseline in cardiac index (CI) with 3.0 mg/kg of enoximone was greater compared to 0.5 and 1.0 mg/kg doses. The arteriovenous oxygen difference (AVO2) was lowered to a greater extent by 3.0 mg/kg dose than the lower doses. C, a greater decrease in right atrial (RA) and pulmonary artery wedge (PAW) pressures occurred with 3.0 mg/kg dose compared to 0.5, 1.0 and 1.5 mg/kg doses. D, the change from baseline in systemic vascular resistance (SVR) with 3.0 mg/kg of enoximone was greater compared to 0.5, 1.0 and 1.5 mg/kg doses. The pulmonary vascular resistance (PVR) decreased to a greater extent with 3.0 mg/kg than the lower doses. E, both stroke volume index (SVI) and stroke work index (SWI) increased to a larger extent with 3.0 mg/kg dose than 0.5 and 1.0 mg/kg doses. F, lower doses (0.5 and 1.0 mg/kg) mildly increased plasma norepinephrine (PNE) whereas the other doses decreased PNE in a somewhat dose-dependent manner. The plasma-renin activity (PRA) increased with lower doses (0.5, 1.0 and 1.5 mg/kg) whereas the other doses produced no change.

ment, then somewhat higher doses may be required. In this context, it should be noted that the hemodynamic studies performed in the supine position may not completely reflect the action of the drug in the upright position, since filling pressures may be somewhat lower and the effect of enoximone more marked in the upright posture. Substantial decreases in filling pressures did occur in some patients at lower doses of enoximone so that the lowest effective dose should probably be instituted in an individual patient. This is particularly important since heart rate increased at all dose levels tested, except for 0.5 mg/kg. Since heart rate is a major determinant of myocardial oxygen consumption, it appears desirable to minimize this upward change. Finally, the hormonal changes in response to enoximone were heterogenous. Smaller doses appeared to activate the renin-angiotensin and sympathetic nervous system to a greater degree than higher doses. If such activation is unwanted, therapy with a larger dose may be appropriate. Caution must be used in the interpretation of our study because we evaluated only the acute effects of a single dose of oral enoximone. Further studies will be needed to determine whether these differential dose effects are present during long-term drug therapy. Nonetheless, our results do indicate that in a given CHF patient, one can individualize the optimal dose of oral enoximone based on the desired change in hemodynamic and hormonal parameters.

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#### **Inotropic Response to Dobutamine in Elderly Patients with Decompensated Congestive Heart Failure**

Michael W. Rich, MD, and Michael Imburgia, MD

ne of the principal effects of aging on the cardiovascular system is an attenuation of responsiveness to  $\beta$ -adrenergic stimulation. Dobutamine, a synthetic catecholamine with potent inotropic properties mediated through stimulation of cardiac  $\beta$  receptors, has been shown to be less effective in elderly patients with either normal left ventricular function<sup>2</sup> or congestive heart failure (CHF) complicating acute myocardial infarction.3 However, although CHF is a leading cause of hospitalization in the elderly, the response to dobutamine in elderly patients with severe, decompensated CHF has not previously been described.

Nine patients ≤70 years of age (group I, mean 55 years, range 18 to 70) and 5 patients ≥80 years of age (group II, mean 83 years, range 80 to 87) with decompensated CHF due to severe contractile dysfunction un-

responsive to conventional therapy were studied. Patients with valvular heart disease or primary diastolic dysfunction were excluded. All patients were admitted to the coronary care unit for invasive hemodynamic monitoring with a pulmonary artery catheter. After baseline hemodynamic measurements were obtained, dobutamine 5 µg/kg/min was initiated. One hour later, hemodynamic measurements were repeated and the dose of dobutamine was increased to 10 µg/kg/min. This was continued for an additional hour, after which a final set of hemodynamic data was acquired.

With the exception of age, there were no significant differences between groups with respect to baseline clinical or hemodynamic characteristics. However, the older patients tended to have more severe renal dysfunction than the younger group (blood urea nitrogen  $52 \pm 25$  vs  $38 \pm 33 \text{ mg/dl}$ ; creatinine  $2.4 \pm 0.8 \text{ vs } 1.6 \pm 0.8 \text{ mg/dl}$ ). In addition, the underlying cardiac pathology was ischemic cardiomyopathy in all 5 group II patients, but this diagnosis was confirmed in only 5 of the group I patients (2 patients had idiopathic dilated cardiomyopathy; 2

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TABLE I Effect of Dobutamine on Hemodynamic Parameters\*

	Group I: ≤70 yrs (n = 9)		Group II: ≥80 yrs (n = 5)			
Dobutamine dose (µg/kg/min) Heart rate (beats/min) Mean arterial pressure (mm Hg) Central venous pressure (mm Hg) Pulmonary artery pressure (mm Hg) Pulmonary wedge pressure (mm Hg) Cardiac output (liters/min) Cardiac index (liters/min/m²) Stroke volume (ml) Stroke volume index (ml/m²) Systemic resistance (Wood units) Pulmonary resistance (Wood units)	0 90 ± 20 84 ± 9 13 ± 7 38 ± 12 24 ± 10 3.6 ± 0.9 2.0 ± 0.4 42 ± 14 23 ± 7 21 ± 6 3.9 ± 1.8	5 97 ± 20 87 ± 10 9.3 ± 3.6 36 ± 10 22 ± 8 5.1 ± 1.2 <sup>†</sup> 2.8 ± 0.4 <sup>§  </sup> 55 ± 17 <sup>†</sup> 30 ± 8 <sup>†</sup> 16 ± 5 <sup>†</sup> 2.6 ± 0.9 <sup>†</sup>	10 100 ± 18 $^{\parallel}$ 84 ± 12 9.1 ± 3.3 36 ± 11 23 ± 8 5.7 ± 1.3 $^{\dagger \pm}$ 3.1 ± 0.4 $^{5 \pm}$ 59 ± 19** 33 ± 9** 14 ± 4 $^{\dagger}$ 2.5 ± 1.1 $^{\dagger}$	0 76±5 90±11 11±5 34±12 26±9 3.3±0.8 1.8±0.3 43±11 24±4 26±8 3.2±2.1	$5$ $81 \pm 7$ $86 \pm 6$ $9.4 \pm 4.8$ $33 \pm 10$ $22 \pm 7$ $4.0 \pm 1.1$ $2.3 \pm 0.5^{\circ}$ $50 \pm 14$ $28 \pm 7$ $20 \pm 5$ $2.8 \pm 1.4$	$10$ $84 \pm 7^{1}$ $81 \pm 14$ $11 \pm 5$ $32 \pm 14$ $18 \pm 10$ $4.1 \pm 1.2$ $2.3 \pm 0.6$ $48 \pm 12$ $28 \pm 6$ $18 \pm 5$ $3.2 \pm 1.6$

\* All values are mean  $\pm$  standard deviation. † p <0.01 vs baseline; † p <0.05 vs proup II; † p <0.10 vs baseline; † p <0.05 vs baseline;

TABLE II Percent Change in Cardiac Index and Stroke Volume Index in Response to Dobutamine

Dobutamine Dose (μg/kg/min)	Group I (≤70 yrs)	Group II (≥80 yrs)	p Value
Cardiac index 0 to 5 5 to 10 0 to 10	+40% +11% +55%	+28% 0 +28%	0.07 0.06 0.01
Stroke volume index 0 to 5 5 to 10 0 to 10	+30% +10% +43%	+17% 0 +17%	0.13 0.05 0.03

patients had no history of myocardial infarction but had not undergone angiography to exclude coronary artery disease). One patient in each group had CHF complicating acute myocardial infarction.

The effects of dobutamine at doses of 5 and 10 µg/ kg/min on measured and calculated hemodynamic parameters are summarized in Tables I and II. In group I patients, dobutamine 5 µg/kg/min produced significant increases in cardiac output and cardiac index and tended to increase stroke volume and stroke volume index while decreasing systemic and pulmonary vascular resistances. When the dose was increased to 10 µg/kg/min, further changes in these parameters occurred and, with the exception of the pulmonary vascular resistance, all were significantly improved relative to baseline levels. In group II patients, salutory effects on hemodynamics were seen with the 5 µg/kg/min dose, but the magnitude of benefit on specific hemodynamic variables was 30 to 40% less than that in the younger patients. In addition, increasing the dose to 10 µg/kg/min produced no further improvement in hemodynamics in group II patients, so that the net change from baseline in cardiac index and stroke volume index was only half as great in the older as in the younger patients (Table II).

In the present study, there were no significant agedependent differences in the effect of dobutamine on arterial and intracardiac pressures, but the augmentation in cardiac output and stroke volume in patients ≥80 years of age was only about half that seen in the younger cohort. In addition, whereas younger patients responded to an increase in dose from 5 to 10 µg/kg/min, older

patients received little additional benefit from the higher dose and some patients actually did worse. One possible explanation for this is that  $\beta$  receptors may be maximally saturated at the lower dose in older patients, so that an increase in infusion rate is unable to further augment cardiac output.

The mechanism for decreased  $\beta$  responsiveness in the elderly has not been fully delineated. It does not appear to be due to tachyphylaxis, reduction in  $\beta$ -receptor density, failure of the receptors to bind catecholamines or inability of the contractile proteins to respond to calcium.1 The latter point is clinically relevant, since it suggests that the efficacy of non-β-agonist inotropic agents may be less age-dependent and that such agents may therefore be useful in managing elderly patients. Preliminary studies with digoxin<sup>4,5</sup> and the bipyridine derivative amrinone<sup>6,7</sup> would appear to support this hypothesis. There is also evidence that the combination of dobutamine and amrinone may be more efficacious than either agent alone.8

In the present study, it is possible that factors other than differences in the inotropic response to dobutamine could account for some of the hemodynamic variance between groups. As noted, whereas all 5 group II patients had ischemic cardiomyopathy, only 5 of 9 group I patients had this diagnosis confirmed. However, when only the group I patients with ischemic cardiomyopathy are included in the analysis, similar trends result: maximum increases in cardiac index and stroke index are 48 and 29%, respectively, in group I patients, compared to only 25 and 13% in group II patients (p = 0.02 for cardiac index, p = 0.09 for stroke index). Thus, differences in etiology of CHF between younger and older patients do not appear to account for the difference in response to dobutamine. A second possible factor is a difference between groups in the use of other medications, particularly diuretics and vasodilators. In conducting this study, maintenance doses of other medications were continued, but dose changes and the addition of new medications were discouraged. During the course of study, 5 group I patients (56%) received vasodilators (including nitrates), compared to 3 group II patients (60%). Similarly, 3 group I patients (33%) received a diuretic, versus 1 group II patient (20%). The use of other medications, including calcium antagonists, antiarrhythmics and digitalis, was

also comparable between groups. Finally, it is possible that differential effects of dobutamine on the vasculature may have influenced the hemodynamic response. Specifically, as seen in Table I, the pulmonary wedge pressure appears to be reduced to a greater degree in the elderly than in the younger patients. This difference is not statistically significant (p ≥0.2) and the lack of decrease in wedge pressure in group I patients is not consistent with prior reports of the effect of dobutamine on this parameter (suggesting that this is a chance finding related to the small sample size). However, it is conceivable that the moderately greater reduction in preload in the older cohort could have contributed to a lower augmentation in stroke volume via the Frank-Starling mechanism. In contrast, the mean arterial pressure is also lowered to a somewhat greater degree in the older patients (also not statistically significant), which might be expected to have a favorable effect on stroke volume (via afterload reduction). Thus, it seems unlikely that these factors are playing a major role in the observed effects of dobutamine on cardiac index and stroke volume index in these patients.

In summary, although the present study is limited by its small sample size and potentially significant differences in baseline variables, the data indicate that the

hemodynamic effects of dobutamine are substantially attenuated in patients ≥80 years of age with decompensated CHF. Furthermore, increasing the dose of dobutamine above 5 µg/kg/min fails to provide additional hemodynamic benefit in this age group.

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#### Long-Term Efficacy and Safety of Coenzyme Q<sub>10</sub> Therapy for Idiopathic Dilated Cardiomyopathy

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oenzyme Q<sub>10</sub> (CoQ<sub>10</sub>) occurs in the mitochondria of human cells. It is 2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone and functions as a cofactor in several enzyme systems related to energy conversion. As such, it is essential for human life to exist. Since mitochondria are very abundant in myocardial cells and because of their huge energy needs, a deficiency of CoQ10 could have a particularly severe effect on myocardial function.

In 1981 we chose cardiomyopathy for clinical study because it has been a disease of unknown cause, which has been apparently limited to the myocardium and has been without effective treatment. A short-term doubleblind cross-over study of 19 patients with cardiomyopathy (New York Heart Association classes III and IV) was completed in 1982. Control subjects' CoQ10 levels that were in the deficiency range were increased into the normal range by oral replacement therapy. This paralleled significant improvement in myocardial function and clinical status. There was no intolerance of the treatment.1

A long-term open-label study was begun in November 1982 with the goal of determining if tolerance of CoQ<sub>10</sub> and clinical improvement were maintained over long periods of time. From our observations with untreated control

subjects in the short-term study and those of Mortensen et al,2 we thought it improper to use untreated control subjects in a long-term study. Myocardial function entails active energy input in both the contracting and relaxing phases, which may not be equally involved in clinical heart disease. Since precise measurement of each phase of myocardial function remains developmental, longterm survival figures could be finite and meaningful.

This long-term study involved patients with chronic dilated cardiomyopathy in New York Heart Association classes II, III and IV. Patients with a history of inflammatory disease involving the myocardium or alcoholism were excluded. Diagnosis was made based on history, physical findings, chest x-ray, electrocardiogram and measurement of myocardial function by analysis of systolic time intervals, echocardiography, radionuclide scans or angiography. All patients had been stable for at least 2 months. After signing informed consent, patients were given CoQ10, 33.3 mg 3 times daily. CoQ10 levels were determined by the method of Vadhanavikit et al,3 and ejection fractions were calculated from systolic time intervals by the method of Weissler et al.4 New York Heart Association classification and survival were recorded. Observations were made at periods of control, 3 months, 6 months and every 6 months thereafter. The patients' conventional therapeutic programs were maintained for at least 2 years.

In the first 42 months, 126 patients entered the study. No new patients were added thereafter, but treatment and observation have continued for over 6 years. There were 77 men and 49 women. Ages ranged from 19 to 80

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TABLE I Mean Changes in Ejection Fraction and Blood Coenzyme Q<sub>10</sub>

	Ejection (%)	Fraction		Blood ( (µg/ml		
Time (Mos)	Mean Value	No. of Patients	p Value	Mean Value	No. of Patients	p Value
0	41	126		0.85	126	
3	55	82	< 0.001	1.99	79	<0.001
6	59	108	< 0.001	2.14	103	< 0.001
12	61	94	< 0.001	2.13	88	< 0.001
18	61	82	< 0.001	2.35	76	< 0.001
24	62	67	< 0.001	2.22	63	< 0.001
30	65	60	< 0.001	1.90	56	< 0.001
36	64	46	< 0.001	1.91	32	< 0.001
42	61	31	< 0.001	1.92	23	< 0.001
48	62	25	< 0.001	2.12	15	< 0.001
54	64	21	< 0.001	1.77	17	< 0.001
60	66	14	< 0.001	1.83	11	< 0.001
66	64	8	< 0.001	1.97	6	<0.001
CoQ <sub>10</sub>	= coenzyn	ne Q <sub>10</sub>	District.		A The	

years with 76% of the patients being in the sixth through eighth decades. The age distribution was the same for both sexes and was similar to that for ischemic heart

Using New York Heart Association criteria, 2% of the patients were in class II, 63% in class III and 35% in class IV.

All patients were symptomatic on entry and were receiving some combination of conventional medications including digitalis (91%), diuretics (82%), afterloadreducing agents (58%), antiarrhythmic agents (35%) and anticoagulants (26%). Angiotensin-converting enzyme inhibitors were being taken by 33% of the patients. Electrocardiograms were normal in 2%, showed left bundle branch block in 44% and nonspecific ST/T changes in 53%. On chest x-ray on entry to the study, 23% had heart size within normal limits, 27% were 1+ enlarged, 36% were 2+ enlarged and 14% were 3+ or 4+ enlarged. By echocardiography, left atrial size, left ventricle size and left ventricular contractility varied from normal to severely enlarged or impaired. Left atrial size was normal in 31%, left ventricular size was normal in 8% and left ventricular contractility was normal in 1%. Coronary angiography and ventriculography had been done in 63%.

In 99% of the patients, the primary complaint was due to myocardial failure with 86% having had documented pulmonary edema. Secondary complaints included severe chest pain in 16%, severe arrhythmia in 40%, thromboembolism in 17% and heart block requiring a pacemaker in 10%.

In 83% of the patients, the diagnosis was first made after congestive heart failure had occurred. Ejection fractions were calculated from the systolic time intervals on entry and were good indicators of the severity of the disease as reflected by heart size on chest x-ray and New York Heart Association class. Ejection fractions were numerically about 15 points higher than those recorded by echocardiography, radionuclide scan and ventriculography.

Mean CoQ10 blood level on entry was 0.85 µg/ml, which was significantly below the mean level of 1.07 µg/ ml for 54 control subjects (p < 0.05). Mean CoQ10 blood levels then rose to approximately 2 µg/ml in 3 months (p <0.001) and remained stable thereafter. The mean ejection fraction was 41% at control and increased to 59% in 6 months (p < 0.001), remaining stable thereafter (Table I). By analyzing the patients individually, it is evident that a significant improvement in the ejection fraction (defined as p <0.05 using the Student t test) occurred in 71% of the patients in 3 months and in 16% in 6 months, totalling 87%. A significant second delayed improvement occurred in 25% of the patients. Only 13% showed no improvement. A total of 106 of 122 patients with at least 1 follow-up or who died before follow-up (87%) improved by 1 or 2 New York Heart Association classes with general but imperfect correlation with improved ejection fraction. Survival was 97, 97, 91, 85, 84, 83, 79, 65, 70, 57, 47 and 52% at 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60 and 66 months, respectively. Death was sudden or due to documented arrhythmia in 38%, pump failure in 31% and noncardiac causes in 31%. Two patients complained of minor itching but otherwise there was no sign or symptom of intolerance in what is now 350 patient years of treatment for patients taking CoQ10 daily for up to 6 years.

Of 17 patients (13%) withdrawn from the study, 29% were class IV and 71% class III. Of the 5 withdrawn for transplant, 4 had been advised earlier to have transplants, but 3 could not qualify. Over a 1- to 2-year period, 4 of 5 improved and were accepted for transplant as qualification standards were modified with time. A fifth patient improved initially, but then deteriorated; all were successfully transplanted. The 4 patients who withdrew for financial reasons were followed 6 to 12 months and 3 were doing very well on CoQ10 obtained over the counter and the fourth had been a responder. Of the 8 patients withdrawn by the primary physician, 6 had been responders, 1 withdrew after a month into the study and I had not improved. It is unlikely that withdrawn patients introduced any bias into the study. It is commonly stated that once cardiomyopathy becomes symptomatic, survival after 2 years is 50%. Survival after decompensation has been reported to be 50% in 1 year.5

The duration of diagnosed disease before entry into the study averaged 19.3 months and varied directly with the severity of disease. Of 9 published cardiomyopathy studies, survival at 6 months varied from 50 to 78% and at 12 months, 35 to 65%.6-14 Clearly, no statistical comparisons can be made, but the results with CoQ10 look very encouraging. Need for hospitalization for cardiovascular problems was about 4 patients/100 patient years and 8/100 patient years from all causes. The majority of deaths occurred in patients who were initially in class IV. The results in class II patients are most encouraging. As far as we can tell all became asymptomatic after CoQ10. The longest time a patient has been treated is 6 years.

Human life requires coenzyme Q<sub>10</sub> for existence. CoQ10 is a unique vitamin similar to niacin in a general biosynthetic concept. The therapeutic activity of CoQ10

will not be like that of digitalis or a diuretic or other conventional drugs for cardiomyopathy. Over 30 years of biochemical research on CoQ10 have revealed that its clinical effectiveness requires the presence of specific apoenzymes, which are proteins with receptors for CoQ10. The fact that 71% of the patients in this study responded in 3 months is presently understood to be based on the time-requiring mechanisms for the biosynthesis of the apoenzymes from DNA and then RNA. The fact that 16% of the patients responded in 6 months may reflect that the 100-mg dosage was too low or that other deficiencies in these patients slowed the therapeutic response to CoQ<sub>10</sub>. The clinical response to CoQ<sub>10</sub> over monthly periods is acceptable in biochemistry for a vitamin in contrast to the almost immediate clinical responses of drugs that act by pharmacologic mechanisms.

CoQ<sub>10</sub> has been demonstrated to be effective and safe for the treatment of patients with dilated cardiomyopathy over a period of 6 years. The thesis that deficiencies in intracellular bioenergetics might be a factor in myocardial failure is strongly supported by these results. Further study could possibly have a major positive impact on myocardial failure from all causes.

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## Prevalence of Significant Congenital Heart Defects in Children of Parents with Fallot's Tetralogy

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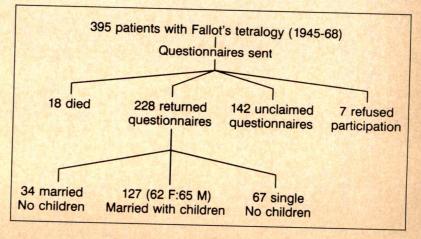
There is a paucity of empiric recurrence risk data for children of patients with some forms of congenital heart defects, especially cyanotic forms such as Fallot's tetralogy (TF). This information is necessary for accurate genetic counseling because many of these patients now reach reproductive age and wish to know the

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risk to their children. This investigation estimates the prevalence of significant congenital heart defects (i.e., those brought to the attention of a medical provider) in children of parents with TF.

Questionnaires were sent to 395 patients with TF who were evaluated at our institution between 1945 and 1968 (Figure 1). These questionnaires addressed the presence or absence of congenital heart defects in children and other first-degree relatives of, as well as pregnancy and miscarriage rates in patients with TF. These patients

FIGURE 1. Flow diagram illustrating questionnaire process and response rate to questionnaire. F = female; M = male.



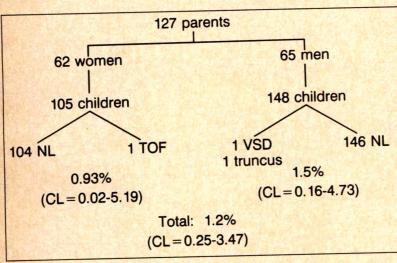
	Families		
No. Children/Family	No.	%	
	44	34.6	
2	54	42.5	
3	21	16.5	
4	4	3.2	
5	2	1.6	
6	2	1.6	
Total	127	100	

were chosen because they were ≥18 years of age. From previous use of questionnaires regarding prevalence of congenital heart defects in siblings and offspring, it is known that subjects tend to overestimate the prevalence, frequently considering "innocent murmurs" to represent congenital heart defects. To avoid this overestimation, very specific questions about the "murmurs" were designed to obviate this problem. The family physician or the pediatric cardiologist who evaluated the child was contacted only if the responses were still ambiguous.

Of the 395 questionnaires mailed, 228 (58%) were returned completed. One hundred forty-one (36%) were returned unclaimed and 7 (2%) subjects refused to par-

ticipate. Eighteen of these patients died, 3 after having 5 reportedly healthy children. These children were excluded because of a lack of detailed information. The mean age of the probands at the time of this questionnaire was  $38 \pm 10$  years (range 24 to 78). One hundred sixty-one of the 228 (71%) subjects were married and of these, 127 (79%) had 1 or more children. No unmarried subjects reported having any children. Of those who were married, 86 were men and 75 were women; no subject had a spouse with a congenital heart defect. Of the 86 married men, 65 (76%) had 148 children and 62 (83%) of the 75 married women had 105 children (Figure 1). The number of children per family is listed in Table I. Twenty of the 62 married women had a combined total of 28 abortions. Twenty-five of these were spontaneous and 3 were therapeutic (for maternal health reasons), for a miscarriage rate of 19.2%, which is within the previously reported range of miscarriage rates for a general population.1,2

Congenital heart defects occurred in 3 (1.2%) of the 253 children; all 3 were girls, 2 of whom had affected fathers and 1, an affected mother. The lesions in the 3 children were truncus arteriosus (1), ventricular septal defect (1) and TF (1) (Figure 2). All lesions were confirmed by a pediatric cardiologist. The children with TF



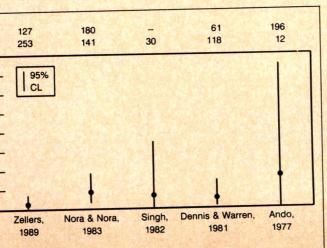


FIGURE 2. Flow diagram illustrating number of children with/without congenital heart disease of male and female patients with Fallot's tetralogy. CL = confidence limits; NL = normal; TOF = tetralogy of Fallot; truncus = truncus arteriosus; VSD = ventricular septal defect.

FIGURE 3. Prevalence of congenital heart defects in children of parents with Fallot's tetralogy from present study and 4 other investigators' results expressed as percent of total children studied. Bars = 95% confidence limits (CL).

Proband, no

Children, no

Prevalence in children,

35

30

25

20

15 10

TABLE II Recurrence Risk of Congenital Heart Defects for Children of Patients with Fallot's Tetralogy

	Proba	nd	CHD in Offsprir	ng					
Study	Gender		M Probands		F Probands		M plus F		
	М	F	CHD/Total	%	CHD/Total	%	CHD/Total	%	CL
Dennis & Warren <sup>3</sup>	36	2	3/71	4.2	0/47	0	3/118	2.5	0.52-7.13
Singh et al <sup>4</sup>	_	_		_			1/30	3.3	0.08-17.22
Ando et al <sup>5</sup>	-	-					1/12	8.3	0.21-38.48
Nora & Nora <sup>6</sup>	-	- L	_	_			6/141	4.2	1.57-9.15
Present study	65	62	2/148	1.3	1/105	0.9	3/253	1.2	0.25-3.47
Total			4/219	2.3	1/152	0.66	14/554	2.5	0.25-5.47

and truncus arteriosus also had autopsy confirmation of their lesion. The child with the ventricular septal defect had experienced spontaneous closure of her defect. There was no apparent relation between the occurrence of congenital heart defects in offspring and the number of offspring per parent or the birth order of the offspring.

The prevalence of congenital heart defects in the siblings and parents of the subjects questioned was 2.3 and 0.43%, respectively. The prevalence in siblings of male and female parents was similar. Only 1 grandparent had a congenital heart defect (patent ductus arteriosus).

The recurrence risk of a congenital heart defect for children of a parent with TF has been reported to be 2.5 to 8.3% (Table II, Figure 3).<sup>3-7</sup> In our study, the largest reported thus far, the recurrence risk of significant congenital heart defects in children is 1.2% and is comparable to that previously reported. Two of the 3 patients with congenital heart defects had conotruncal abnormalities.

The recurrence risk in siblings of patients with TF has been assessed by several investigators<sup>3,5,8-10</sup> and found to be consistent with the multifactorial mode of inheritance, with a recurrence risk of 2%. In the present study, the recurrence risk was 2.3% for siblings of probands, similar to that reported by other investigators (Table III). This suggests that our ascertainment of affected relatives is good.

The reasons for these discrepancies in recurrence risks in children born to parents with congenital heart defects in our study and the risks quoted in those studies by Whittemore, 11 Rose, 12 Emmanuel 13 and their associates are unclear. Ascertainment bias, local environmental factors and chance are possible reasons for this. For example, in Whittemore's prospective study, it is possible that patients invited to participate who already had several healthy children may have declined participation. In the retrospective studies, many patients were not located; it may be more likely that patients with affected children would remain in contact with the medical center. Finally, the studies by Whittemore, 11 Rose, 12 Emmanuel 13 and their associates did not specifically address recurrence risk in children of patients with TF.

A potential weakness in the study design of this investigation is that the children were not examined by the investigators. This could result in an underestimation of recurrence risk, especially for subtle lesions such as bicuspid aortic valve. However, all children were examined by their own pediatrician and many have been examined by

**TABLE III** Recurrence Risk of Congenital Heart Defects for Siblings of Subjects with Fallot's Tetralogy

		Siblings	Siblings with CHD			
Authors	Probands	Total No.	No.	%	CL	
Boon et al <sup>8</sup>	100	189	4	2.1	0.58-5.3	
Ando et al <sup>5</sup>	196	380	6	1.6	0.54-3.26	
Sanchez-Cascos <sup>9</sup>	113	327	4	1.2	0.36-3.38	
Dennis & Warren <sup>3</sup>	61	100	0	0	0-3.62	
Nora & Nora <sup>10</sup>	157	338	9	2.7	1.12-4.95	
Present study	228	567	13	2.3	1.15-3.69	
Total	855	1,901	36	1.9	1.15 5.05	

pediatric cardiologists (especially if they had cardiac murmurs). It is unlikely that significant cardiac abnormalities would have been overlooked. Also, it has been demonstrated in a large cohort study<sup>14</sup> that 88% of congenital heart defects are diagnosed by 1 year of age and 98% are diagnosed by 5 years of age. Only 5.5% of the children from this study were younger than 1 year. To prevent overdiagnosis by inclusion of patients with innocent or functional murmurs,<sup>15</sup> very specific questions relating to these murmurs were included in the questionnaire. Cardiologists evaluating these murmurs also were contacted when, despite these questions, ambiguity still existed. All suspected innocent murmurs were confirmed to be innocent by these physicians. Thus, we think overdiagnosis is unlikely.

These data are similar to previous reports of recurrence rate of congenital heart defects in children of parents with TF and represent the largest study of parents with TF. This information will be useful for counseling patients with TF regarding their risk for having a liveborn child with a significant congenital heart defect.

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#### Depressed Left Ventricular Systolic Ejection Force in Hypothyroidism

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xperimental hypothyroidism is associated with depressed myocardial contractile function, possibly due to alterations in contractile protein isoforms. 1,2 Abnormal systolic performance has been demonstrated in humans with severe, primary hypothyroidism; replacement of thyroid hormone leads to normalization of systolic time intervals in these patients.3 Recently, a new Doppler method of noninvasively determining left ventricular (LV) ejection force was described.4 Using Newton's second law of motion, force may be derived from the product of the mass and acceleration of blood ejected out the aortic valve. This study tests the hypothesis that this new noninvasive method can detect subtle changes in LV systolic function in patients with primary hypothyroidism.

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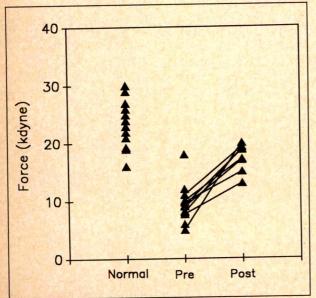


FIGURE 1. Systolic ejection force (kdyne) in 12 normal subjects and 12 hypothyroid patients (pre). Follow-up data from 8 hypothyroid patients after thyroid replacement are also shown (post). Systolic force increases after thyroid replacement (p <0.001) but is still significantly less than normal (p <0.01).

Twelve outpatients (11 women and 1 man) with newly diagnosed idiopathic hypothyroidism were studied. The ages of the patients ranged from 35 to 68 years. The diagnosis of hypothyroidism was based on typical clinical symptoms (as determined by the patient's internist) and a thyrotropin level >15 µU/ml. Patients with histories of cerebrovascular or cardiovascular disease were excluded. No patient was taking diuretics, antiarrhythmic agents, vasodilators or other cardiovascular medications.

A Hewlett Packard 77020 AC/AR ultrasonoscope device with a 2.5-MHz transducer was used for all studies. Pulsed-wave Doppler sampling of the LV outflow tract was performed in the apical 5-chamber view with the sample volume located just beneath the aortic valve leaflets. Doppler echocardiographic studies were repeated after thyroid replacement in 8 patients. Patients were considered to be euthyroid if their clinical symptoms resolved and serum thyrotropin had fallen to <7 \(\mu U/ml.\) The mean time of treatment to establish euthyroidism was 23 weeks; follow-up echocardiograms were performed <3 weeks after the demonstration of euthyroidism. Echocardiographic data were analyzed using a Cardiology Workstation (GTI Freeland Medical Division). LV mass, volumes and ejection fraction were calculated as previously described.5 Systolic force was determined as previously described.4 Systolic force values from the patients were compared to those of 12 normal volunteers with no history of cardiovascular or thyroid disease. The 2-sample Student t test was used to compare patients with normal subjects and the paired Student t test was used to analyze the effects of thyroid replacement; a p value < 0.05 was considered to be statistically significant.

All patients and normal volunteers had normal echocardiograms except 1 patient who had a trivial pericardial effusion that resolved after thyroid therapy. There were no significant differences in heart rate, end-systolic or end-diastolic volume index, ejection fraction or systolic blood pressure after thyroid replacement (Table I). There was a small but significant increase in diastolic blood pressure after thyroid replacement.

The systolic force in normal volunteers was  $23 \pm 4$ kdyne. In patients with hypothyroidism, systolic force was markedly abnormal before thyroid replacement

when compared to 12 normal subjects (p < 0.001) (Figure 1). After thyroid replacement, systolic force increased significantly (p <0.001); however, it remained significantly decreased when compared with normal subjects (p < 0.01).

This study demonstrates that systolic force is abnormal in patients with hypothyroidism even when LV ejection fraction is normal. These data suggest that under some circumstances noninvasive measurement of systolic force may be a more sensitive measure of contractile dysfunction than ejection fraction.

The early systolic force as measured by the Doppler method is actually the net force vector in the direction of the aorta; LV force is opposed by a retrograde force from central aortic pressure. Thus, the systolic force parameter would be expected to be sensitive to afterload conditions. For example, if aortic blood pressure increased and total LV force remained unchanged, the net early systolic force would decrease. In this study, there was no decrease in blood pressure that could explain the significant increase in measured early systolic force after thyroid replacement, suggesting a primary increase in myocardial con-

The persistently abnormal values of systolic force after thyroid replacement suggest a possible persistent myocardial contractile dysfunction. It is unlikely that this result is due to abnormally high values in our normal volunteers, as our normal volunteers had lower values than those described by Isaaz et al.4 It is possible that, early after biochemical euthyroidism is achieved, alterations in cardiac proteins induced by hypothyroidism have not been completely reversed. This might be particularly true of structural proteins that have long half-lives,

**TABLE I** Clinical and Echocardiographic Characteristics Before and After Thyroid Replacement

	Before (n = 12)	After (n = 8)	p Value
Heart rate (beats/min)	68 ± 11	75 ± 10	NS
Systolic BP (mm Hg)	127 ± 10	140 ± 18	NS
Diastolic BP (mm Hg)	81 ± 9	86±9	0.04
Mass index (g/m²)	$109 \pm 17$	$114 \pm 29$	NS
ESVI (ml/m²)	20 ± 5	19±6	NS
EDVI (mI/m <sup>2</sup> )	50 ± 10	50 ± 9	NS
EF (%)	59 ± 5	64±9	NS
Force (kdyne)	9±3	17±2	<0.001

P values represent results of Student's f test using paired data from 8 patients. BP = blood pressure; EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; NS = not significant.

#### which may require a longer period of biochemical euthyroidism to return to normal.

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#### False-Negative Diagnosis of Proximal Aortic Dissection by Computed Tomography or Angiography and Possible Explanations Based on Transesophageal Echocardiographic Findings

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cute dissection of the thoracic aorta is a life-A threatening disorder and early diagnosis is mandatory. Correct diagnosis must include the precise proximal origin of aortic dissection (AD) since patients with type I and II AD (DeBakey classification) usually require immediate surgery, whereas patients with type III AD can often be treated medically.1 For the detection of AD, angiography, computed tomography (CT) and transesophageal echocardiography (TEE) are well established.2-5 All these techniques may be associated with false-negative findings, that is, complete failure to visualize any AD at all or incorrect assessment of the proximal AD extension. We examine possible explanations for in-

complete or false-negative AD diagnoses by CT or angiography using information provided by TEE studies.

From 1984 to 1988, 29 patients in this hospital with AD underwent TEE; in addition, all 29 patients had been studied either by angiography (n = 23), by CT(n = 23)or by both. (In some patients these examinations were performed at district hospitals.) Six other patients in whom the diagnosis of AD was based on TEE alone were excluded. Two patients who died before either CT or angiography were also excluded. Of the remaining 27 patients, 21 underwent surgery and 6 were treated medically. In all patients undergoing surgery, TEE diagnosis could be subsequently confirmed.

CT studies were performed at our hospital after repeat intravenous bolus injection of contrast material (Siemens Somatom). Angiography was performed after transfemoral insertion of a pigtail catheter using either standard (n = 9) or digital subtraction mode (n = 14).

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**TABLE I** Transesophageal Echocardiographic, Computed Tomographic and Angiographic Findings in Seven Patients with Acute Thoracic Aortic Dissection

Pt	Type of Aort	tic Dissection (Del	Bakey Classification)			
	TEE*	СТ	Angiography	Explanations		
1		111	W	Large entry tear in the ascending aorta with rapidly pendulating		
2		111		intimal flap and similar blood flow in true and false lumina		
3	i	III	_			
4		?	?	Almost complete thrombotic obliteration of the false lumen		
5	1	?				
6	II.	?				
7	1	111	N. C.	Heavy CT artifacts due to a trachestoma steel cannula		

\* TEE findings proven by subsequent surgery.

CT = computed tomography; TEE = transesophageal echocardiography; — = not performed; ? = uncertain diagnosis.

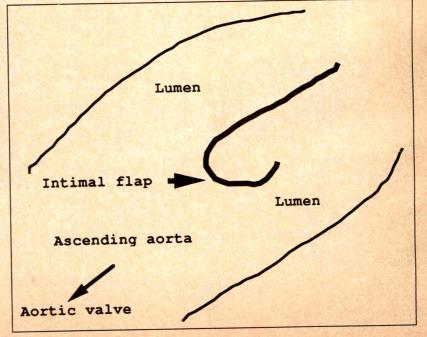
For TEE studies, a 3.5- or 5.0-MHz phased array transducer system was used (with incorporated Doppler in 19) mounted at the tip of a modified gastroscope (Diasonics Echoscope, Diasonics Inc., or Hewlett Packard, model 21362A). All patients were studied in a left lateral decubitus position without any complications as described previously. Before the TEE examination, patients received a local pharyngeal anesthesia (1% lidocaine spray) and a mild intravenous sedation (diazepam 5 mg) to avoid an inappropriate blood pressure increase.

Comparison between TEE and angiographic findings revealed complete agreement in 20 of 22 patients (10 type I, 4 type II, 6 type III AD); 18 of the 22 patients subsequently underwent surgery and the diagnoses were confirmed. Comparison between TEE and CT findings revealed complete agreement in 15 of 22 patients (7 type I, 1 type II, 7 type III AD); 17 of the 22 patients subsequently underwent surgery and the diagnoses were confirmed. Seven patients showed discrepancies between TEE and CT or angiographic findings (Table I); these patients subsequently underwent surgery, which con-

firmed the TEE findings. Three patients (nos. 1 through 3, Table I) showed a large entry tear in the ascending aorta close to the arch (Figure 1; patient no. 2) with rapidly pendulating intimal flap and blood flow in the true and false lumina of comparable intensity. TEE provided an unequivocal diagnosis whereas CT and angiography missed the proximal AD involvement in 3 patients and I patient, respectively, resulting in the false diagnosis of type III AD. In 3 patients (nos. 4 through 6, Table I), there was an almost complete thrombotic obliteration of the false lumen. Thrombosis could clearly be identified on the CT scan or angiogram; however, CT as well as angiography failed to identify a dissecting membrane. In contrast, color Doppler TEE allowed the visualization of the intimal flap around the thrombotic material as well as the identification of small entry tears in areas where the thrombotic obliteration was still incomplete. In the last patient (no. 7, Table I), a steel cannula in the tracheostoma created such heavy artifacts on the CT scan that the ascending aorta could not be adequately imaged.



FIGURE 1. Transesophageal echocardiogram of the ascending aorta close to the aortic arch showing a large entry tear and a pendulating intimal flap (patient no. 2, Table I); note that the blood flow in both the true and false lumen is virtually identical as documented by the color-coded Doppler signal.



Our results point out that certain conditions may lead to incomplete or wrong angiographic or CT findings in patients with AD. These conditions consist, at first, of at least 1 entry tear large enough to provide similar blood flow in the true as well as false lumina, thereby preventing the identification of any temporal and densitometric differences in contrast enhancement, which are the most specific signs of AD by angiography or CT.2-4

Second, as soon as the false lumen is completely filled with thrombotic material, a clear delineation of the intimal flap may be obscured on the CT scan or angiogram; however, thrombosis of the aorta may occur in conditions other than dissection (e.g., thrombosis of true aneurysm). Finally, the image quality of CT scans may be impaired by artifacts due to surgical clips, prosthetic devices, pacemaker wires or, as in a patient presented here, to the cannula of a tracheostoma.

TEE may have certain limitations in the diagnosis of isolated short-distance type II AD due to the trachea obscuring a small region of the ascending aorta. In a

recently published multicenter trial, no false-negative or false-positive TEE results were found in the area of the aortic arch and the descending aorta.5

The present report indicates that diagnosis of proximal AD extent using CT or angiography may be difficult at least in some patients with large entry tears or complete thrombosis of a lumen. Artifacts may also affect CT image quality. TEE may overcome the diagnostic difficulties under these conditions.

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#### Right Ventricular Myocardial Mass Quantification with Magnetic **Resonance Imaging**

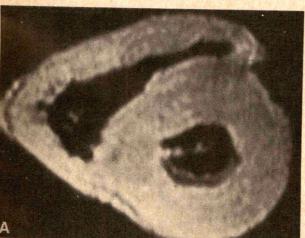
Edward S. Mackey, MD, Martin P. Sandler, MD, Robert M. Campbell, MD, Thomas P. Graham, Jr., MD, James B. Atkinson, MD, PhD, Ronald Price, PhD, and Gordon A. Moreau, MD

lterations of right ventricular (RV) size and shape are common in both congenital and acquired cardiopulmonary disease. Noninvasive quantification of RV mass could enhance the assessment of various hemodynamic overloads in such patients, as well as response to treatment. Left ventricular mass can be estimated using magnetic resonance imagery, 1-3 echocardiography, 4 xray transmission computed tomography,5 single photon emission computed tomography6 and contrast ventric-

ulography. 7 RV mass has been estimated invasively in a single report8 and a single abstract has been published measuring RV mass by x-ray transmission computed tomography.9 Gated magnetic resonance imagery provides excellent detail of cardiac anatomy10-12 through the use of orthogonal planes, as well as angled views that simulate echocardiographic imaging planes. This study evaluates magnetic resonance estimation RV mass in vitro.

Twelve formalin-fixed, structurally normal human hearts obtained at necropsy from patients aged 1 day to 77 years were studied. Causes of death were trauma (5), chronic medical disorders (4) and congenital defects (3). Each heart was removed after great vessel transsection.

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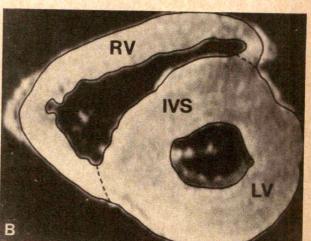


FIGURE 1. A, cross-sectional cardiac nuclear magnetic resonance image in (A) left ventricular short-axis plane. B, same image as in A with hatched borders included to define digitized right ventricular plus ventricular septal areas. IVS = interventricular septum; LV = left ventricle; RV = right ventricle.

Postmortem clots were removed and gauze placed to maintain chamber lumen. Hearts were perfused with 10% formalin at 40 mm Hg for 24 to 48 hours. This fixation procedure can change heart weight by 2 to 3% without exceeding 5%.13 Imaging was performed using a 0.5-Tesla superconducting magnetic resonance scanner (Technicare). Images were T1 weighted with the pulse repetition frequency 500 ms and the echo interval 38 ms. Hearts were placed in a 28-cm head coil (256-mm field of view) and imaged in the left ventricular short axis plane from apex to base (Figure 1A). Slice thickness equaled 3 mm. Total slices varied with heart size from 10 to 20 slices. Pixel size was 1 × 2 mm; this set the minimum pixel area uncertainty to 20 mm<sup>2</sup>, which was considered insignificant relative to other factors. A gadolinium phantom was present in each image for real space correlation. Images were photographed using a 2× magnification factor to improve border identifica-

100 90 80 70 (dm) 60 estimate 50 IMR=0.95(A)+0.72 SEE= 5.6gm 40 SEE = 5 r = 0.98 NMR 30 n=12 20 10 90 100 30 40 50 60 70 80 20 anatomic mass (gm) A 250 225 200 estimate(qm 175 NMR=,94(A)+2.81 SEE=11.8gm 150 r=0.99 n=12 125 100 NMR 75 50 25 60 90 120 150 180 210 240 270 300 B anatomic mass (gm)

FIGURE 2. The comparison of anatomic mass (axis) to NMR (nuclear magnetic resonance) imaging-estimated mass (ordinate) for right ventricle (A) and left ventricle (B) plus ventricular septum, respectively. The dashed line represents line of identity. SEE = standard error of the estimate.

The ventricular endocardial and epicardial borders were traced using a Compaq Deskpro computer with Summagraphics Summasketch digitizing board. For each image, the RV free wall was separated from left ventricular free wall and the interventricular septum during tracing by following the arc of the interventricular septum continuous to the left ventricular epicardium. The left ventricular epicardial and endocardial borders were defined as the outer edge of signal intensity. All papillary muscles were considered part of the myocardium. RV borders were defined as areas of uniform intensity. Any areas of intensity not continuous with the endocardium were not included in the tracing. Epicardial fat was excluded from analysis. Figure 1B shows a representative image with the digitized borders shown.

Ventricular mass was calculated as follows: for each slice, endocardial area was subtracted from epicardial area. The resulting ventricular slice area was multiplied by the slice thickness (3 mm) to obtain slice volume. Slice volume was multiplied by the specific density of cardiac muscle (1.055 g/cc3) to give slice mass. The

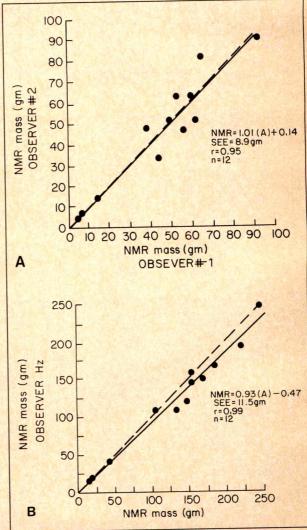


FIGURE 3. Interobserver variability for NMR imagingestimated right (A) and left (B) ventricular mass. Dashed line represents line of identity. Abbreviations as in Figure 2.

TABLE	Analysis of \	/entricular Mass (g	1)
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		Right Ventric	le		Left Ventricle			
		NMR				NMR		
Pt Age (yrs)	Anatomic	Observer 1*	Observer 2	Anatomic	Observer 1*	Observer 2		
1	Newborn	4.7	4.8	4.8	14.0	16.4		
2	0.67	6.5	6.4	6.6	19.8		16.1	
3	3	14.1	14.8	13.8	44.9	18.0	17.5	
4	37	41.1	38.5	48.6		41.8	40.8	
5	66	42.0	44.2		125.0	133.8	109.0	
6	45	56.9		33.3	112.8	106.3	109.0	
7	17	57.5	61.5	51.9	195.2	185.0	167.9	
8	77		53.0	63.3	227.0	221.5	194.6	
9		58.2	60.1	63.4	152.4	148.6	121.5	
	22	63.6	56.0	46.3	157.0	155.5	150.6	
10	34	65.0	56.2	81.7	165.0	170.2		
1	67	66.4	50.0	51.1	195.1		150.6	
12		92.7	92.6	91.1	258.1	155.0 248.5	146.8 248.0	

NMR = mass as estimated using nuclear magnetic resonance imaging.

estimated mass for each ventricle was calculated by summing consecutive slices from apex to base.

Images for each heart were traced independently by 2 observers to determine interobserver variation. To determine intraobserver variation, observer no. 1 repeated the measurements several days later.

After magnetic resonance imagery analysis, the measured anatomic ventricular mass was obtained. All epicardial fat and large epicardial coronary arteries were removed from the ventricular muscle. Atria were removed by dissecting along the atrioventricular groove; all valves and anular rings were then removed. The RV free wall was separated from the left ventricular free wall and the interventricular septum as described. Each ventricle was dried and weighed separately.

Standard linear regression was used to compare anatomic mass to magnetic resonance mass as measured by observer no. 1 and to express interobserver variability (observer no. 1 vs observer no. 2). Intraobserver variability (observer no. 1) was expressed as percent mean absolute variation divided by mean magnetic resonance mass.

Patient data and ventricular mass are summarized in Table I. RV mass ranged from 5 to 93 g; left ventricular plus ventricular septal weights varied from 14 to 258 g. Anatomic and magnetic resonance ventricular mass correlated well for both the right ventricle and left ventricle plus ventricular septum (Figure 2A and B).

Interobserver variability, depicted in Figure 3A and B, showed a close correlation. Intraobserver (observer no. 1) variability was 2% for both right ventricle and left ventricle plus ventricular septum.

The present study demonstrates that RV mass can be accurately and reproducibly estimated in autopsied human hearts using magnetic resonance imagery. Arcilla et al<sup>18</sup> estimated RV mass using a combined echocardiographic/angiographic technique, but this method has not been duplicated or applied clinically. Technical problems have complicated RV mass evaluation using echocardiography alone. The substernal location of the RV does not permit consistent delineation of this chamber and the irregular RV endocardium is seldom clearly outlined.

An in vitro study was deemed an essential intermedi-

ate study for assessing sources of errors in magnetic resonance RV mass estimation prior to in vivo experiments. In vitro estimates eliminate errors due to motion blurring, which includes errors resulting from irregular heart rates and images acquired during motion. In vitro determinations also minimize uncertainties due to edge definition. With in vivo imaging, surrounding tissues and blood within the chambers produce signal levels above the background noise level and thus necessitate the development of an intensity-level criterion that is "defined" to be the ventricular edge. In vitro imaging produced high-contrast edges in which the ventricular boundary is defined to be pixel values above background. Problems in differentiating epicardial fat, papillary muscles and interventricular septum are common to both in vitro and in vivo determinations. The results of this study should, therefore, be interpreted as the minimum volume errors which can be achieved using magnetic resonance imaging methods with the specified image resolution and slice thickness for ventricular volume estimates. The ability to obtain resolution satisfactory for crisp edge detection for accurate RV volumes and mass analysis in vivo remains unproven.

In this study, a slice thickness of 3 mm was chosen to minimize partial volume effects created by oblique sectioning. Partial volume effects may cause errors in mass evaluation through difficulties in defining endocardial and epicardial borders. The imaging plane for this study was perpendicular to the long axis of the left ventricle. Coupled with the narrowed slice thickness, these angled views help to minimize left ventricular partial volume effects. Due to the complex geometric configuration of the right ventricle, there are no standard orthogonal views for RV imaging and the use of narrow slice thickness allows for more reliable and reproducible RV mass determinations.

Recent studies indicate that left ventricular hypertrophy, together with abnormal ventricular function, may serve as a substrate for arrhythmia. <sup>14</sup> Likewise, Garson et al <sup>15</sup> have reported an increased risk for serious ventricular arrhythmias in postoperative tetralogy of Fallot patients with residual RV hypertension and dysfunction. Thus, the noninvasive estimate of RV mass would provide a

powerful new method to aid in overall assessment of a patient's response to abnormal right heart hemodynamics, as well as providing further insight to possible correlations between mass and significant ventricular arrhythmias.

The RV and left ventricular mass values resulting from this study will serve as a baseline for subsequent in vivo studies. Substantial improvements in magnetic resonance imaging will be needed before the type of accuracy reported herein can be reproduced with in vivo studies.

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#### Atrial Standstill After Treadmill Exercise Test and Unique Response to Isoproterenol Infusion in Recurrent Postexercise Syncope

Yusuke Tamura, MD, Osamu Onodera, MD, Kunio Kodera, MD, Yutaka Igarashi, MD, Takashi Miida, MD, Yoshifusa Aizawa, MD, Tohru Izumi, MD, Akira Shibata, MD, and Satoshi Takano, MD

radycardia associated with Bradycardia application occurs relatively rarely after exercise testing,1 and is considered to be a form of vasovagal reaction. Although it is usually benign, extremely rare cases with cardiac standstill have been reported.2 We recently examined a man with recurrent postexercise syncope who developed atrial standstill after a treadmill test. We present the results of his treadmill exercise tests repeated under different conditions and the result of an isoproterenol infusion test, which provided insights into the mechanism of this reaction.

A 45-year-old Japanese man had had recurrent syncopal attacks af-

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ter strenuous exercise, such as rope skipping, since he was 40. He underwent a maximal treadmill exercise test as an outpatient for the evaluation of syncope. The test was performed according to the Bruce protocol and terminated after 12 minutes due to fatigue. At about 1 minute into recovery while he was standing, cardiac standstill emerged on the electrocardiographic monitor. He lost consciousness, but was successfully resuscitated.

On admission, his electrocardiogram showed a short PR interval (0.12 second) and strain patterns in leads I, aVL and V<sub>3</sub> through V<sub>6</sub>. Echocardiography showed concentric left ventricular hypertrophy without any features of outflow tract obstruction. Left ventricular ejection fraction determined by contrast angiography was 68%, but end-diastolic pressure was elevated to 30 mm

Hg. Coronary arteriography was normal except for systolic compression of the left anterior descending coronary artery. Neither Holter monitoring nor an overdrive suppression test revealed evidence of sinus node dysfunction. His response to the Valsalva maneuver was normal.

A second treadmill test was performed after inserting a pacing lead into the right ventricle and was stopped after 12 minutes with an attained heart rate of 170 beats/min without ST-segment changes. At about 1 minute and 20 seconds into the recovery phase, his heart rate suddenly decreased and was replaced by a slow ectopic atrial rhythm (Figure 1). Pacing was started, and no P waves were seen for nearly 30 seconds. Sinus rhythm returned at 5 minutes into recovery. During pacing, his systolic blood pressure was 48 mm Hg while standing and remained as low as 80 mm Hg in the supine position (Figure 2A). When a cooling down period of 3 minutes was added after exercise at a speed of 1 mph, neither bradycardia nor hypotension occurred (Figure 2B). They also did not occur

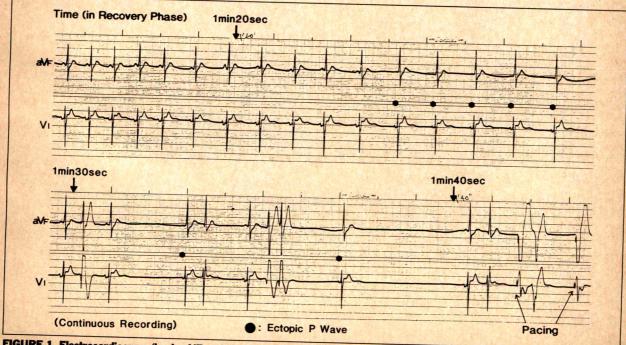


FIGURE 1. Electrocardiogram (leads aVF and  $V_1$ ) after the second treadmill test, showing postexercise bradycardia. Ventricular premature complexes are also noted. Ventricular pacing was started at about 1 minute and 40 seconds into the recovery phase.

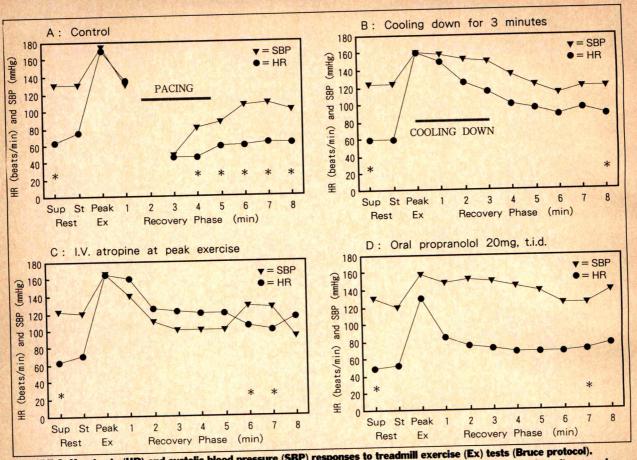


FIGURE 2. Heart rate (HR) and systolic blood pressure (SBP) responses to treadmill exercise (Ex) tests (Bruce protocol).

Asterisks indicate that the patient was in the supine (Sup) position. A, the patient developed vasovagal reaction after exercise.

The blood pressure remained low despite pacing. The pacing rate was kept at less than 50 beats/min to help recognize the patient's spontaneous rhythm. B, when atropine was given at peak exercise, the blood pressure in the recovery phase was lower than at rest and exhibited significant postural changes. C, cooling down in the postexercise period prevented vasovagal reaction.

D, oral propranolol suppressed peak heart rate to 130 beats/min and prevented vasovagal reaction. St = standing.

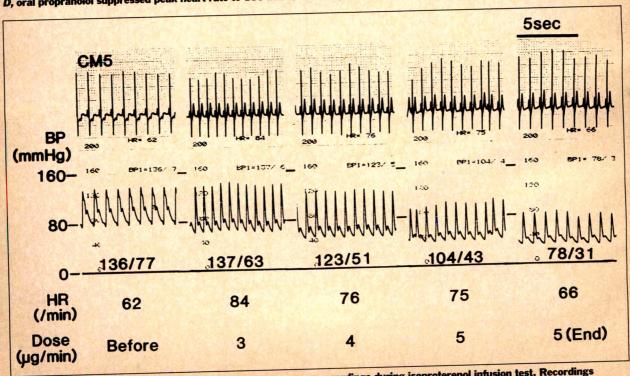


FIGURE 3. Electrocardiogram (CM<sub>5</sub>) and radial artery pressure recordings during isoproterenol infusion test. Recordings obtained at dosages of 1 and 2  $\mu$ g/min are not shown. BP = blood pressure; HR = heart rate.

when the supine position was assumed after exercise. Intravenous atropine (0.04 mg/kg) given at peak exercise prevented bradycardia but its protective effect against hypotension was only partial (Figure 2C). Oral propranolol (20 mg, 3 times daily) resulted in a peak exercise heart rate of 130 beats/min and a normal response in the recovery phase (Figure 2D), as well as premature cessation of exercise at a heart rate of 145 beats/min.

An isoproterenol infusion test was performed with the patient in the supine position (Figure 3). The dosage was 1 µg/min initially, and increased by 1 µg/min every 3 minutes up to 5 µg/min. Heart rate increased from 62 beats/min at baseline to 84 beats/min at a dosage of 3 µg/min and blood pressure changed from 136/77 to 137/63 mm Hg. Surprisingly, both heart rate and blood pressure decreased at dosages of 4 and 5 µg/min. At the end of the test, the heart rate decreased to 66 beats/ min and the blood pressure to 78/31 mm Hg.

The mechanism of vasovagal reaction is not completely understood. Vasodilation seems to occur independently of bradycardia because in this patient, as stated in other reports, 3,4 intravenous atropine and ventricular

pacing failed to restore blood pressure. It has often been postulated that sympathetic hyperactivity precedes the vasovagal reaction. 1,2,4,5 A mechanism deduced from the experimental study by Oberg et al5 is that activation of the left ventricular mechanoreceptors through left ventricular cavitary obliteration reflexly stimulates the vasodepressor center, leading to increased vagal tone and sympathetic withdrawal. Both an increase in contractility due to heightened sympathetic tone and a reduction in preload contribute to cavitary obliteration. In this patient, the role of preload was obvious because his postexercise response was unremarkable when a cooling down period, as well as a supine position, was prescribed after exercise. Increased chamber stiffness due to left ventricular hypertrophy might have contributed to reduction of preload.

The mechanisms through which propranolol prevented vasovagal reaction may be 2-fold: depression of left ventricular contractility, and inhibition of  $\beta$ -adrenergic-mediated vasodilation preserving venous return. Recent clinical studies have shown that enhanced sympathetic activity leads to vasovagal reaction.3,6 In these reports isoproterenol induced bradycardia and hypoten-

sion in prone patients, but only when they were upright.<sup>3,6</sup> In contrast, our patient developed bradycardia at high dosages of isoproterenol when he was supine. It is known that vasovagal reaction also occurs spontaneously in the supine position on some occasions such as emotional stress or acute blood loss.4 Therefore, it is likely that some patients with vasovagal reaction develop vagotony even in the supine position under isoproterenol infusion, if it augments ventricular contraction to a certain degree or reduces preload through its vasodilative property.

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# Limited Research Funds and Cardiac Medicine Without Cardiac Surgery

ad times have befallen the National Institutes of Health (NIH). Although NIH's total budget rose steadily during the 1980s (in constant dollars it increased by 50% between 1981 and 1990), the number of new and renewable grants funded dropped sharply in 1989 and will plunge again in 1990 (Figure 1). Although some of the new monies have been allocated to national priorities such as AIDS (\$300 million in 1990) and the human genome project (\$59 million in 1990), the major explanations for the drop in funding of new and renewable grants are the increased number of grants awarded in previous recent years, the increase in average cost of each grant, and the increase in average length of each research project. The number of new and renewable grants that received funding went from 5,493 to 6,477 from 1984 to 1987 and the average length of each project went from 3.3 to 4.1 years from 1983 to 1988. Thus, research projects approved in previous years are soaking up most of the available grant money, and little is left to launch new ones.

Federal medical research monies are not being allocated in proportion to the magnitude of the problems. According to the National Center for Health Statistics, in the USA in 1989 AIDS will cause about 34,400 deaths, cancer about 494,400, and heart disease 777,630 deaths. In contrast to these death totals, federal spending in fiscal 1989 for research and education in AIDS will amount to \$1.3 billion, for cancer \$1.4 billion, and heart disease, \$1.0 billion.

The National Heart, Lung, and Blood Institute (NHLBI) has been hard hit. Only 13% of its approved grants will be funded this year and of those funded, the numbers of dollars allocated will be 13% less than the amount approved. The intramural program (the on-campus research program) of the NHLBI also is being hard hit. A big item in the intramural budget is that spent for pa-



tient care, and nearly 60% of the \$17 million so spent is for cardiac surgery. Thus, the elimination of cardiac surgery would free up a sizable amount of money for research in other NHLBI laboratories. And that's what was done. The Surgery Branch will discontinue clinical activities in June 1990 and research activities in June 1991.

But can a broad clinical research program in heart disease exist without cardiac surgery? Can cardiology be strong in the absence of cardiac surgery? I think not. Unfortunately, with certain notable exceptions like systemic hypertension, most symptomatic heart diseases are best treated by surgery because most heart diseases produce mechanical blood flow problems. Congenital heart disease (with its defects in cardiac septa or abnormal communications or connections between vessels or cardiac chambers or obstruction at, below or above cardiac

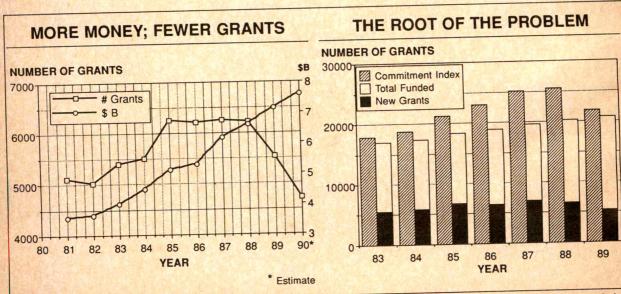


FIGURE 1. NIH's total budget rose steadily during the 1980s, but the number of new and competing grants dropped sharply in 1989 and it will plunge again in 1990. The budget figures are in current dollars. In constant dollars, NIH's budget increased by 50% between 1981 and 1990.

50% between 1981 and 1990.

As the number of new grants increased in the mid-1980s, NIH took on a commitment that it could not keep. Until 1988, the commitment index, calculated by multiplying the number of new grants by their average length, rose much faster than the total number of grants NIH could support. Reproduced with permission from Palca J, Science 1989(November 24);246:988.

valves) is definitively treated only by surgery. Valvular heart disease (with its obstructions and leaks) is definitively treated only by surgery. Coronary artery disease today is more definitively treated by surgery than by other means. Pericardial disorders often require surgery. The cardiac catheterization laboratory is purely a diagnostic one—not a therapeutic one—without cardiac surgery readily available. Treatment of heart disease today requires both cardiology and surgery and centers without both will, in my view, not be major centers for long. The intermingling of specialists in cardiac medicine and in cardiac surgery under the same roof is essential for the

proper development of each.

So Surgery at the National Heart, Lung, and Blood Institute is going because the money is needed elsewhere for more "high-risk research." (Other reasons given for its demise also include the "changing nature of the cardiology research programs," the "inability to recruit and maintain a permanent cadre of qualified surgeons," and "program priorities.") The entire NIH budget in 1990 is about \$7.5 billion. In contrast, the Defense Department's budget currently is \$302 billion—nearly 30% of the entire federal budget. By contrast, \$249 billion is spend on Social Security, \$181 billion on interest payments, and \$99 billion on Medicare. Of the \$302 billion defense budget, \$86 billion is spent for operations and maintenance—the cost of keeping troops in the field and maintaining weapons; \$85 billion for procurement—the cost of weapons and other supplies; \$79 billion for payroll and retirement benefits, and \$38 billion (5 times the NIH budget) for research and development on new weapons systems. The cost of the M-1 battle tanks (\$1.9 billion) is nearly twice that of the entire NHLBI budget. The cost of the F/A-18

A Hornet jet fighter planes (\$2.2 billion) is over twice the NHLBI budget. The cost of the F-16 Falcon jet fighter planes (\$3.3 billion) is over 3 times the NHLBI annual budget. The United States share of NATO costs is now \$130 billion, over a third of the entire Defense Department budget, and some estimate that  $60\phi$  of every dollar in our \$302 billion defense budget is devoted to the defense of Europe. Over 50 years after the end of World War II the USA still has 305,000 troops in Europe. And now after the crumbling of the Berlin Wall and of the Communist regimes in Eastern Europe, the cold war is over. Troops must come home. Resources must be reallocated.

To discontinue cardiac surgery and its potential research arm in the largest cardiac research center in the world because 11 million dollars could better be used elsewhere is a statement to cardiac surgeons the world over that surgeons are no longer players in the cardiac investigative world. In actuality, there is no better research laboratory for human beings than the operating room. When cardiac surgery goes, cardiac medicine will soon follow for obstructed coronary arteries or cardiac valves or intracardiac defects or maldirected blood flow usually require operative therapy. Mr. President, a few less M-1 battle tanks every year and a major cardiac research center will prosper, not fade away.

William C. K

William Clifford Roberts, MD Editor in Chief

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CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.
2. Preexisting gallbladder disease (See WARNINGS)

 Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities bewantinus. I. Because or chemical, pharmacological, and clinical similarities between genfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to genfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 2000 pleases treated without the set of the property of the project of jects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects Jecis and 3000 pracebo-treated subjects, but twice as many clotibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated then in a composite the process of treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056). In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell During the Helsinki Heart Study and in the 11/2 year follow-up period since the trial

in the placebo group (difference not statistically significant). This includes 5 basal carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths

from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on course see mation on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the place bo group, a 55% excess for the gemfibrozil group). A 150% excess for the gemiliprozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% ex-cess). This result did not differ statistically

from the increased incidence of cholecystectomy observed in the WHO study in the

from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

A. Concomitant Anticoagulants — Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts — Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. Initial Therapy—Laboratory studies should be done to ascertain Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with

of male rats treated with gemiliprozil at 10 times the human dose.

PRECAUTIONS. 1. Initial Therapy — Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. Continued Therapy — Periodic determination of serum limits should be obtained.

in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. Continued Therapy — Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. Drug Interactions — (A) Lovastatin: Rhabdomyolysis has occurred with combined gemifibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemifibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. Carcinogenesis, Mutagenesis, Impairment of Fertility — Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

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from controls in the incidence of liver tumors, but the doses tested were lower than tho shown to be carcinogenic with other fibrates

Male rats had a dose-related and statistically significant increase of benign Leydig ce tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or tentimes the human does to make the first to the contract of the proximately three or tentimes the human does to make the first to the contract of the proximately three or tentimes the human does to make the first to the contract of the proximately three or tentimes the human does to make the first to the contract of the proximately three or tentimes the human does to make the first to the contract of the proximately three or tentimes the human does to make the first to the contract of t

Administration of approximately three or ten times the human dose to male rats for 10 weel resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that the effect was reversed after a drug-free period of about eight weeks, and it was not transmit

(gemfibrozil) 600-mg Tablets

RAISES HDL...DRAMATICALLY

REDUCES HEART ATTACK

ted to the offspring.

5. **Pregnancy Category B** — Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those pa-

male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

tients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. Nursing Mothers — Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. Hematologic Changes — Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration. Lopid administration.

8. Liver Function — Abnormal liver function tests have been observed occasionally

during Lopid administration, including eleva-tions of AST (SGOT), ALT (SGPT), LDH, bili-rubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

 Use in Children – Safety and efficacy in hildren have not been established. ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study. 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in

the Lopid group (placebo incidence in pasin the ses): gastrointestinal reactions, 34.2% (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fabrical forms of the lopid group (placebo incidence in pasin the Lopid group (placebo incidence in pasin the Lopid group (placebo incidence in pasin the Lopid group (placebo incidence in subjects in the Lopid group (placebo incidence in pasin the Lopid group (plac

(nistologically confirmed in most cases where data are available), 1.2% (Ub%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study. Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of musculoskeletal symptoms (See WARNINGS), and to abnormal liver function tests and hematologic changes (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients. Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

by system. These are categorized according to whether a causal relationship to treat-

by system. These are categorized according to whether a causal relationship to the ment with Lopid is probable or not established:
CAUSAL RELATIONSHIP PROBABLE: Gastrointestinal: cholestatic jaundice; Central CAUSAL RELATIONSHIP PROBABLE: Gastrointestinal: cholestatic jaundice; Central Nervous System: dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; Eye: blurred vision; Genitourinary: impotence; Musculoskeletal: myopathy, myasthenia, myalgia, painful extremities, arthralgia, synoyilis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); Clinical Laboratory: increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; Hematopoiatic: anemia leukopenia bone marrow hyopolasia, eosinophilia: Im-Hematopoietic: anemia, leukopenia, bone marrow hypoplasia, eosinophilia; Immunologic: angioedema, laryngeal edema, urticaria; Integumentary: exfoliative der

munologic: angioedema, laryngeal edema, uriicaria; integumentary. exioliative del-matitis, rash, dermatitis, prunitus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: General: weight loss; Cardiac: extrasys-toles; Gastrointestinal: pancreatitis, hepatoma, colitis; Central Nervous System: confu-sion, convulsions, syncope; Eye: retinal edema; Genitourinary: decreased male fertility; Clinical Laboratory: positive antinuclear antibody; Hematopoietic: thrombocytopenia; Impunologic: anaphylaxis. Lugus-like syndrome, vasculitis: Integumentary: alopecia. Clinical Laboratory: positive antinuclear antibody; Hemantopoietic: thrombocytopenia; Immunologic: anaphylaxis, Lupus-like syndrome, vasculitis; Integumentary: alopecia. DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal. MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur. References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. N Engl J Med 1987;317:1237-1245. 2. Manninen V. Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. JAMA 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.): The Metabolic Basis of Inherited Disease, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.

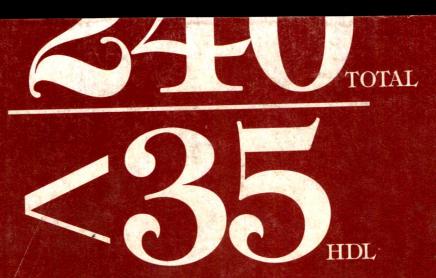
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## What's a common denominator of most heart attack victims?

Mixed hyperlipidemias—elevated cholesterol and triglycerides—are common among heart attack victims,1 and nearly two thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.2

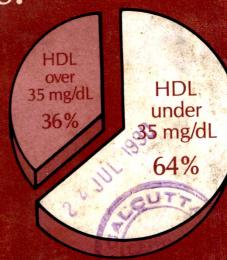
HEART ATTACK PATIENTS (PROCAM TRIAL)<sup>2</sup>

#### LOPID raised low HDL 25%

—in patients whose baseline HDL was below 35 mg/dL in the landmark Helsinki Heart Study (HHS).

#### Reduced heart attack incidence\* up to 62%

-in these HHS patients and 45% in HHS patients whose baseline HDL was below the median (46.4 mg/dL). Incidence of serious coronary events was similar for LOPID and placebo subgroups with baseline HDL above the median (46.4 mg/dL).3



# A powerful case for

#### RAISES HDL...DRAMATICALLY REDUCES HEART ATTACK

LOPID is indicated for reducing the risk of coronary heart disease (CHD) in Type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequand nicotinic acid.

\*Defined as a combination of definite coronary death and/or definite myocardial infarction.

References: 1. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. J Clin Invest. 1973;52:1533-1543. 2, Assmann G, Schulte H. PROCAM-Trial: Prospective Cardiovascular Münster Trial. Zürich: Panscientia Verlag; 1986:8-9. 3. Data on file, Medical Affairs Dept, Parke-Davis.

Please see adjacent page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

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